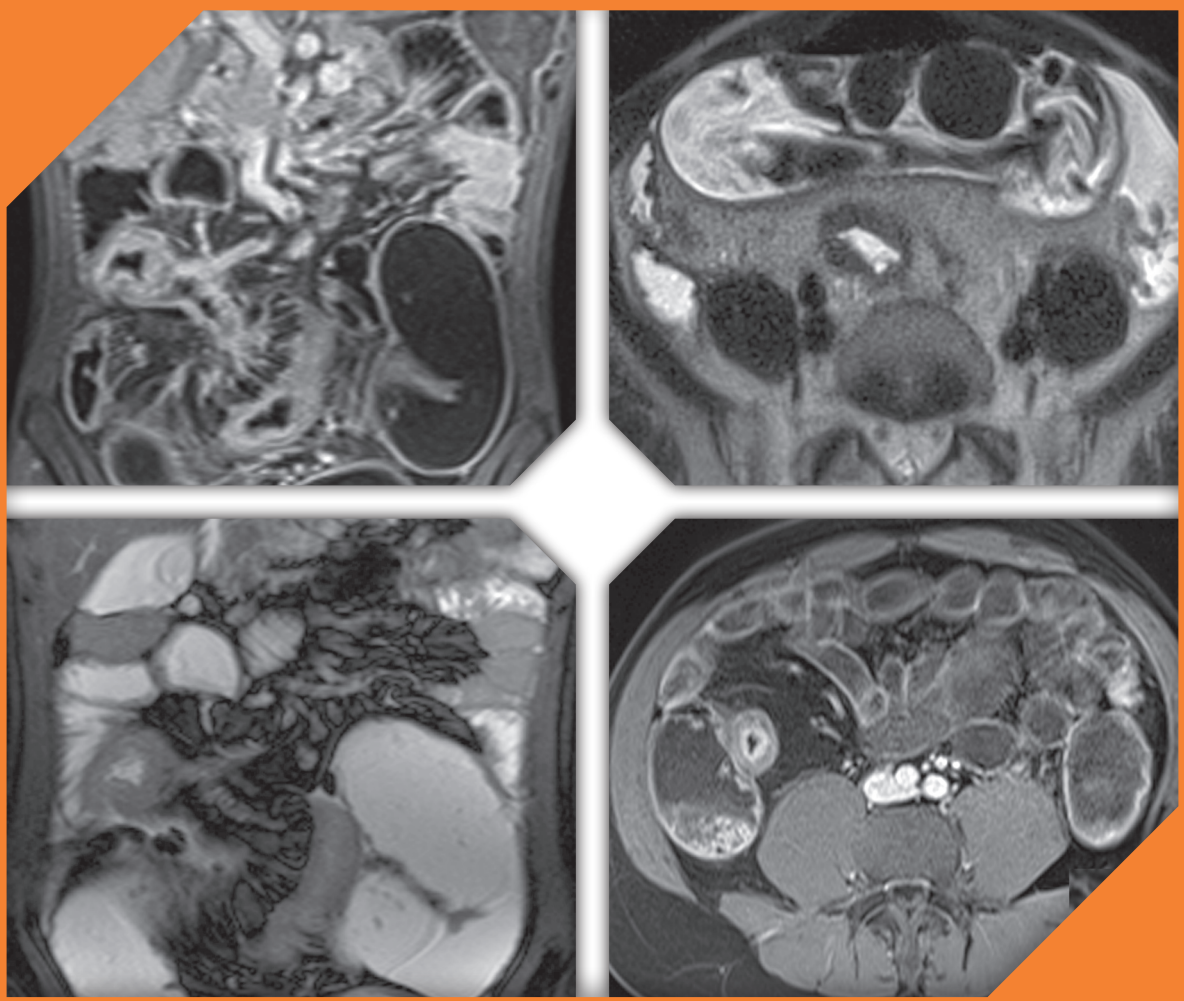
Faculté de Médecine

Université de Liège

Apport de l'entero-colo IRM dans le suivi de la maladie de Crohn: nouvelles perspectives

Paul Meunier



Thèse présentée en vue de l'obtention du titre de « Docteur en Sciences Médicales »
Année académique 2014 - 2015

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Paul Meunier

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Jury interne
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Jury externe
Professeurs Yoram Bouhnik et Etienne Danse

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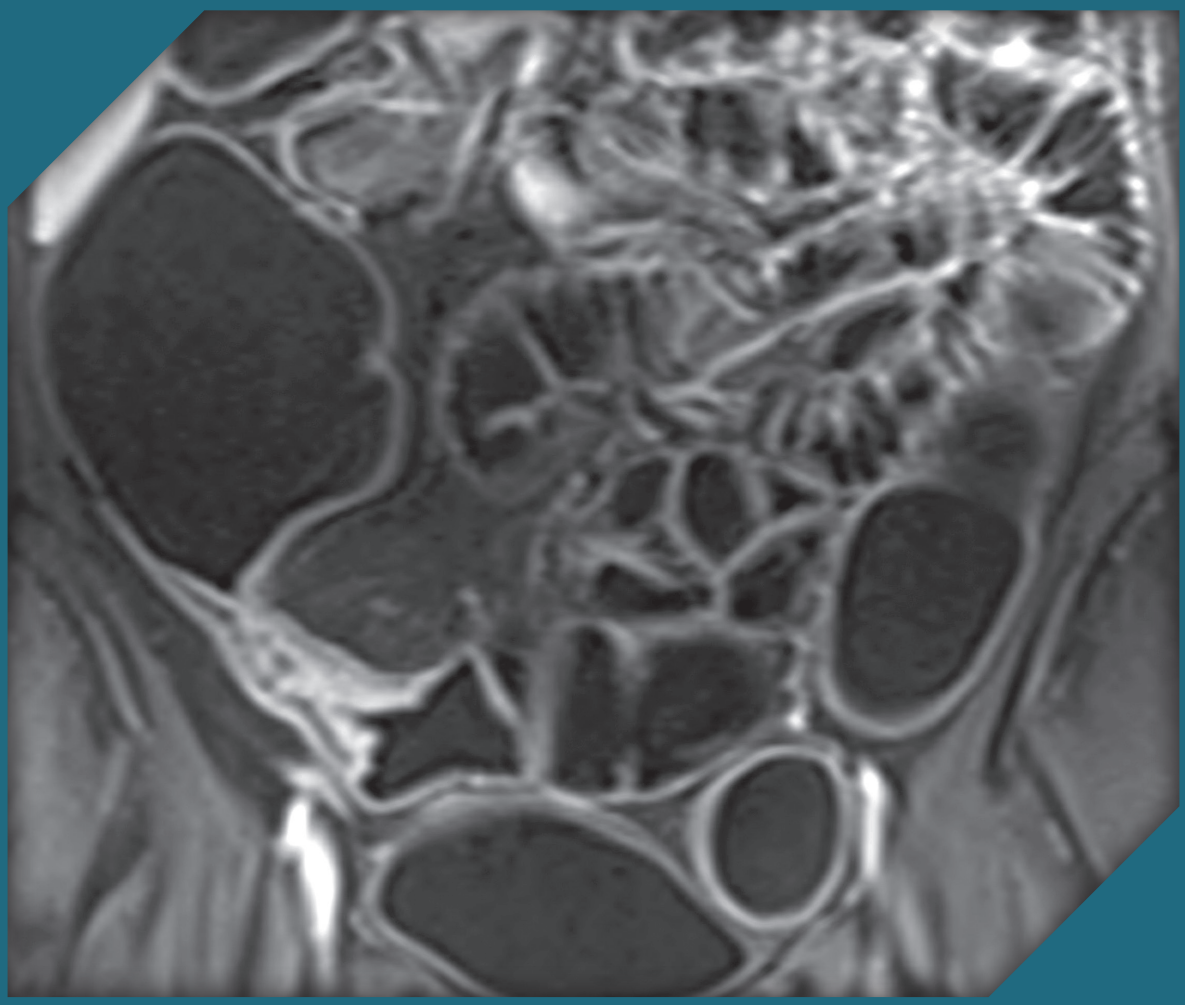
Preambule



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Paul – mai 2015

" Le drame serait de ne pas tenter l'impossible,
de rester, une vie entière, à la mesure de ce qu'on peut. "

Christiane Singer

" Il faut avoir beaucoup étudié pour savoir peu. "

Montesquieu

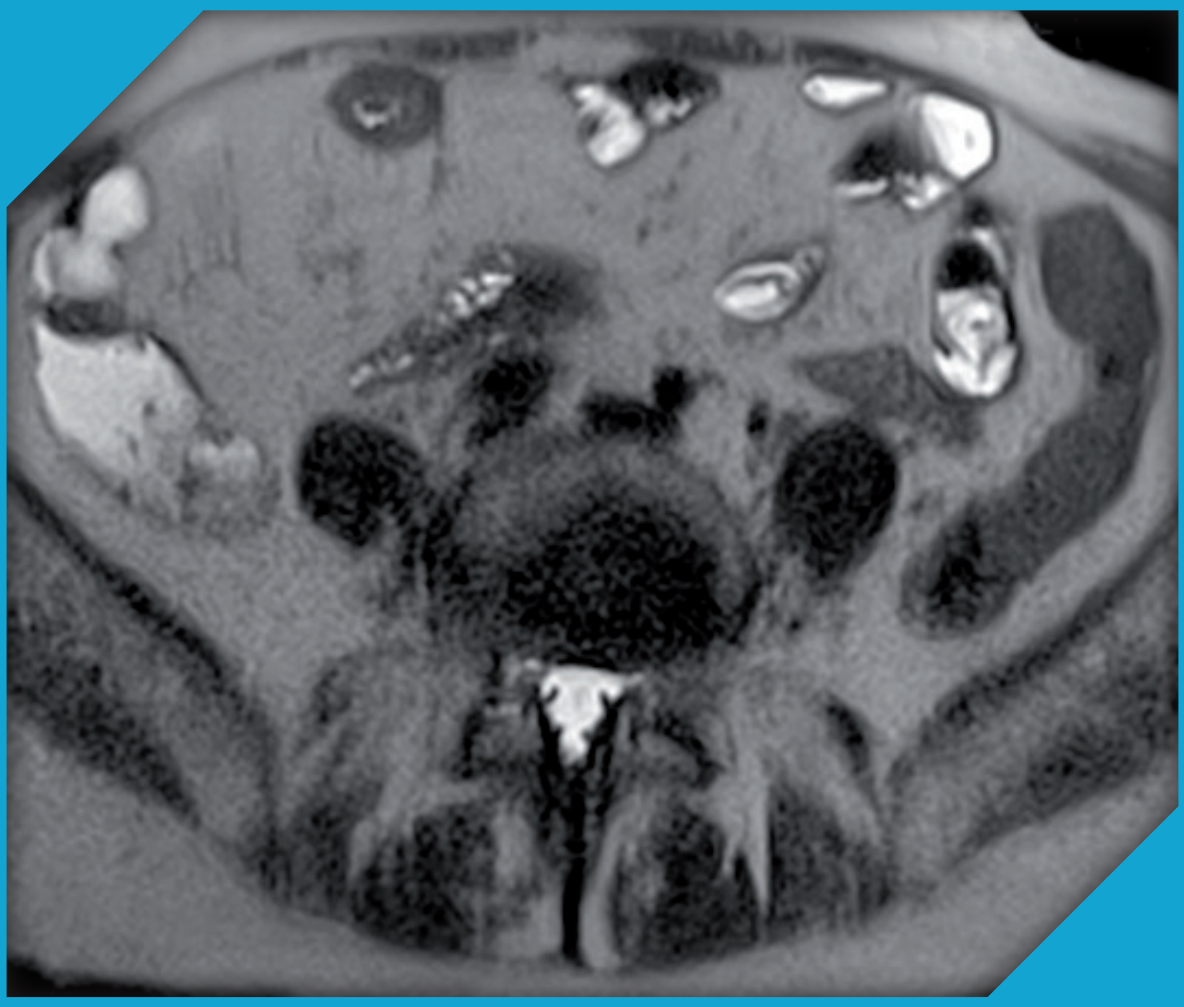
TABLE DES MATIERES

GLOSSAIRE

^{18}FDG	^{18}F-Fluoro-Deoxy-Glucose
3D GE	3D spoiled Gradient Echo *(VIBE)*
bSSFP	balanced Steady-State Free Precession *(TrueFISP)*
CDAI	Crohn's Disease Activity Index
CRP	C-Reactive Protein
CT	Computed Tomography
DWI	Diffusion Weighed Imaging
ecMR	entero colo MR
Fat Sat	Fat Saturation
HBI	Harvey –Bradshaw Index
IRM	Imagerie par Résonance Magnétique
IV	Intraveineux, Intraveineuse
MaRIA	Magnetic Resonance Index of Activity
MR(I)	Magnetic Resonance (Imaging)
PACS	Picture Archiving and Communication System
PET	Positon Emission Tomography
SS-ETSE	Simple-Shot Echo Train Spin Echo *(HASTE)*
TNF	Tumor Necrosis Factor

Aux patients atteints de la maladie de Crohn

Introduction generale



ETAT DE LA QUESTION

La maladie

1. Histoire naturelle[1]

La maladie de Crohn est une maladie chronique du tractus digestif, touchant le plus souvent des sujets jeunes et évoluant sur un mode alternatif de poussées et de rémissions[2, 3, 4].

Si l'on n'en connait pas précisément la cause, il est maintenant communément admis qu'elle a pour origine une réponse immunologique aberrante orientée contre la flore intestinale chez des individus génétiquement prédisposés.

De multiples gènes de susceptibilité ont été mis en évidence. Ces gènes pourraient non seulement contribuer à la prédisposition à la maladie mais aussi en influencer le profil clinique et l'évolution[2].

Malgré leur intérêt et leur rôle potentiel dans des outils de prédiction avec d'autres marqueurs, les marqueurs génétiques ne seront probablement jamais seuls prédicteurs de l'évolution à cause de l'implication de multiples facteurs environnementaux[3]. Le facteur environnemental le mieux documenté est le tabagisme qui représente à la fois un facteur de risque de développement de la maladie et un facteur augmentant l'agressivité et le risque de récidive notamment postchirurgicale de celle-ci[2, 5].

La maladie se caractérise par une réponse inflammatoire chronique classiquement de type granulomateux (bien que les granulomes ne soient pas détectés à l'histologie chez 30 à 50% des patients).

La réaction immune est complexe et perpétue la réponse inflammatoire menant au développement de lésions généralement ulcérées, superficielles ou plus profondes. Ces lésions, classiquement transmurales, peuvent toucher tous les segments du tube digestif, de la bouche à l'anus.

Sur le plan clinique, l'expression est très hétérogène et dépend de la localisation et du type de lésion. Des lésions grêles étendues donneront de la dénutrition; des lésions coliques donneront une diarrhée aqueuse et parfois sanglante ; des lésions sténosantes donneront des tableaux occlusifs ou subocclusifs ; des lésions pénétrantes donneront des fistules et des

abcès intraabdominaux ; des lésions rectales et périanales donneront des suppurations de la région.

La maladie peut rester évolutive tout au long d'une vie, 80% des diagnostics étant posés avant l'âge de 40 ans. Les maladies diagnostiquées chez le sujet jeune sont souvent plus sévères et plus délabrantes[2]. Un retard de diagnostic n'est pas rare compte tenu du caractère peu spécifique de certains symptômes, d'un début parfois sournois et très progressif de la maladie ou encore sous forme de manifestations extradigestives.

Sur le plan de la localisation, si, comme rappelé plus haut, n'importe quel segment peut être atteint de la bouche à l'anus, il existe une nette prédilection pour l'iléon distal et le colon proximal *(Fig. 1)*. L'atteinte digestive supérieure (essentiellement œsogastroduodénale et grêle proximale) est rarement isolée chez les patients caucasiens, et rentre plutôt dans le cadre d'un phénotype oriental (chinois).

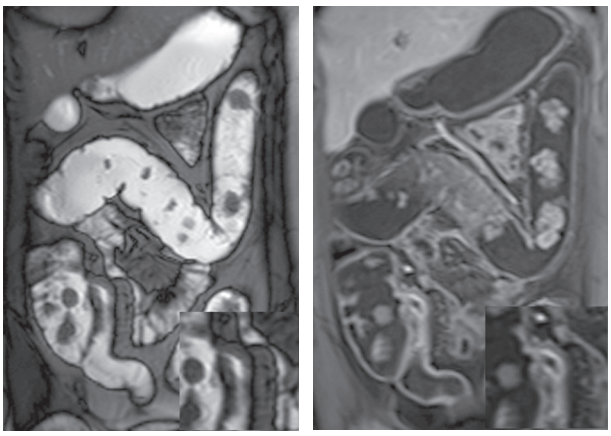


***Fig. 1**: Atteinte iléo-caecale aigüe non compliquée. A gauche, en T2, à droite en T1+C.*

En termes de comportement, la maladie de Crohn est une atteinte chronique, persistante et destructrice, perforante et/ou sténosante, menant à la nécessité de résection chirurgicale chez près de la moitié des patients au total et chez près de 80% des patients avec atteinte iléale. Sa progression peut être ralentie par les traitements médicamenteux *(Fig. 2)*.

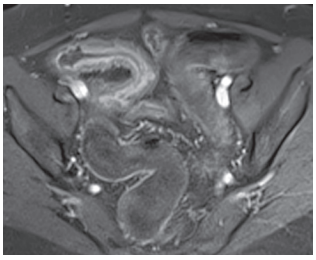


***Fig. 2**: Maladie très active, atteinte aigüe distale. T1+C.*

L'évolution n'est pas nécessairement linéaire. Elle peut aussi se présenter d'emblée comme une maladie complexe et extensive dans laquelle les récurrences sont difficilement prévisibles et sans cause formellement identifiée.

La rémission permet rarement un retour ad integrum et les poussées inflammatoires laissent le plus souvent place à des remaniements chroniques, souvent fibrosants et parfois sténosants *(Fig. 3)*.

L'activité de la maladie et sa sévérité sont les deux paramètres principaux dans la mise en œuvre du plan thérapeutique.

L'évolution peut être lente ou rapide, intense ou infra-clinique, variable en fonction des patients ou même chez un patient donné au cours du temps. Selon les études de population, 40-50% des patients auront une forme relativement bénigne ne nécessitant pas de traitement immunosuppresseur ou biologique et pas de résection chirurgicale ou une résection courte iléale terminale. L'autre grosse moitié des malades se répartit en formes d'emblée agressives (20%) par leur étendue, localisation et/ou le caractère pénétrant des lésions et en formes de sévérité croissante (30%) se révélant progressivement au cours de l'évolution.

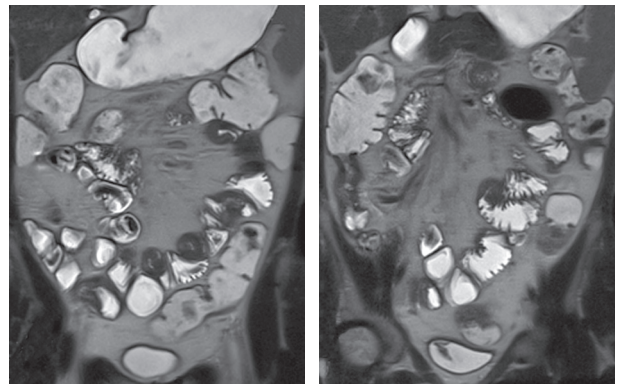


***Fig. 3**: Sténoses cicatricielles étagées – T2.*

Le nombre réduit de traitements disponibles et leur caractère parfois lourd et/ou contraignant impose, de façon primordiale et fondamentale, à chaque étape de la maladie, une évaluation rigoureuse, précise et complète du status lésionnel permettant de définir une stratégie adaptée à chaque patient et privilégiant un rapport bénéfice/risque optimal[5]. Depuis l'avènement des traitements anti-TNF qui permettent une cicatrisation endoscopique (muqueuse) des lésions, cette cicatrisation est devenue un objectif thérapeutique. Au-delà de cela, et au-delà du simple contrôle symptomatique, c'est l'absence de progression des lésions et le contrôle du dommage tissulaire qui est visé. Des interrogations subsistent toutefois concernant l'utilisation de la cicatrisation endoscopique comme objectif thérapeutique. Elles concernent principalement le degré de cicatrisation à obtenir pour avoir un impact favorable sur l'histoire naturelle de la maladie et des lésions qui la caractérisent. Après quelle durée de traitement cette cicatrisation doit-elle être atteinte et contrôlée? Une cicatrisation partielle de la muqueuse est-elle suffisante ? Des lésions résiduelles superficielles peuvent-elles être tolérées ? Quelle est la fréquence et la signification de la persistance de lésions transmurales voire extramurales, non détectées à l'endoscopie ? Ces questions traduisent d'une part le manque de données sur le sujet, mais d'autre part aussi les limites intrinsèques de l'endoscopie qui ne peut évaluer que la surface interne (muqueuse) de la paroi intestinale dans une maladie classiquement transmurale voire extramurale. Dans ce contexte, l'imagerie en coupes pourrait être d'un apport majeur. Le CT scanner étant pénalisé par son caractère irradiant, l'échographie par l'obstacle des interférences gazeuses et des zones mal visualisées (en profondeur), l'IRM se détache comme un outil adéquat. L'IRM est en effet une technique d'imagerie en coupes non irradiante, possédant une excellente définition de contraste et capable d'analyser le tube digestif dans toute sa longueur et toutes les couches de la paroi intestinale ainsi que les lésions extramurales.

2. Outils d'évaluation objective de la maladie, en particulier par imagerie

Si les signes cliniques et symptômes ont longtemps constitué la base du suivi des patients atteints de la maladie de Crohn, tant du point de vue des indications des explorations diagnostiques que des choix thérapeutiques, il apparaît de plus en plus clairement que la corrélation entre la clinique et le status lésionnel intestinal est faible[3].

La mise au point et le suivi de la maladie requièrent donc, outre une approche clinique précise et régulière, une utilisation des techniques biologiques, endoscopiques et d'imagerie.

2. 1. La biologie

Les biomarqueurs représentent actuellement une alternative très intéressante dans le suivi de la maladie de Crohn, en corrélation et en alternance avec les techniques endoscopiques et d'imagerie.

Parmi eux, la CRP et la calprotectine fécale ont été les plus étudiées[3].

La CRP est produite par le foie et, dans la maladie de Crohn, par le mésentère au site d'inflammation.

La calprotectine est produite au niveau du site inflammatoire également par les polynucléaires neutrophiles, les monocytes et les cellules épithéliales[6, 7].

Elles se majorent en cas d'inflammation, même modérée.

Elles ont des utilités multiples[6-15]:

- confirmation de l'activité (sensibilité de l'ordre de 80% et spécificité de l'ordre de 70%) avant la décision d'une exploration complémentaire ou d'une modification de traitement, ce qui permet d'éviter des examens inutiles et des retards dans les modifications thérapeutiques;
- monitoring thérapeutique rapide et efficace;
- confirmation de la cicatrisation muqueuse par corrélation avec l'endoscopie et/ou l'imagerie (efficacité limitée, voisine de 60%, en combinaison des deux), et plus sûrement chez les patients à taux négatif au départ;
- prédiction de la rechute avec une avance de 3 à 4 mois sur les phénomènes cliniques, avec une efficacité de l'ordre de 60-70%.

La CRP apparaît comme le reflet de l'activité extrapariétale[8].

La calprotectine constitue plus un marqueur de l'atteinte muqueuse[10,11].

Dans le suivi postopératoire, la CRP semble jouer un rôle minime, mais le dosage de la calprotectine apparait prometteur.

2. 2. L'endoscopie

Si l'utilisation rationnelle de différents critères cliniques et biologiques participe à l'établissement de certains scores d'activité, l'endoscopie est actuellement la technique d'approche morphologique considérée comme la référence pour l'évaluation précise du caractère, du nombre et de l'étendue des lésions muqueuses.

Comme mentionné plus haut, elle présente toutefois plusieurs limites dont voici les principales[3]:

- elle est invasive et relativement coûteuse;
- elle ne permet pas facilement l'exploration complète du grêle;
- elle n'aborde que le versant endoluminal des sites lésionnels alors que les lésions pariétales extra-muqueuses, et extra-pariétales sont fréquentes (épaississement pariétaux, fistules, abcès, remaniements mésentériques…);
- le degré de cicatrisation muqueuse à obtenir n'est pas établi.

C'est en raison de ces limitations que l'imagerie peut représenter un moyen d'investigation complémentaire très intéressant, principalement l'imagerie en coupes.

2. 3. L'imagerie [1, 4, 16]

Nous allons passer en revue succinctement les différentes techniques disponibles et leur place par rapport aux besoins des patients et des cliniciens référents.

1. **La radiologie conventionnelle avec contraste baryté**, et plus particulièrement le transit baryté du grêle, a longtemps constitué l'examen de première intention dans la mise au point de la maladie de Crohn. Modérément invasif (entéroclyse), peu coûteux et facile d'accès, il était jusqu'il y a quelques années l'examen « de base » dans l'évaluation de l'étendue et de l'intensité de la maladie. En raison de son caractère irradiant (même modéré) et du fait qu'il ne permette pas l'évaluation de l'expression transmurale de l'atteinte ni qu'il ne montre plus d'anomalies (fistules, sténoses…) que d'autres techniques, il est devenu un examen de troisième intention dont les indications résident essentiellement dans la mise en évidence de fines lésions muqueuses (exemple : lésions aphtoïdes) et dans l'appréciation d'anomalies fonctionnelles (transit - péristaltisme).

2. **L'examen échographique**, même si l'accessibilité des segments atteints peut lui être limitée par les conditions techniques et notamment la profondeur à laquelle ils se trouvent, reste une alternative intéressante, tant dans le diagnostic initial (conditions d'urgence par

exemple - douleurs abdominales aspécifiques - recherche d'abcès) que dans le suivi de lésions connues *(Fig. 4)*.

Il diminue le délai diagnostique et permet d'éviter d'inutiles interventions chirurgicales[17].

Faut-il rappeler ses qualités principales d'innocuité et de disponibilité ainsi que ses limites (tant sur le plan physique que sur celui de l'opérateur) ?

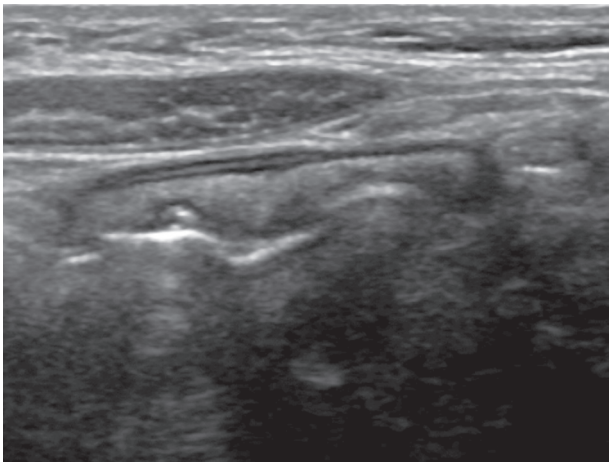


***Fig. 4**: Iléite distale aigüe.*

Il présente aussi un intérêt non négligeable sur le plan de l'étude vasculaire (doppler)[18] et s'avère donc capable, dans des mains compétentes, d'établir un premier bilan, le plus complet et précis possible.

Récemment, l'usage des produits de contraste (microbulles) s'est considérablement développé, avec des potentialités extrêmement intéressantes.

Les données de la littérature montrent un intérêt particulier de l'analyse, non seulement qualitative (doppler couleur) mais également quantitative de la vascularisation pariétale, ce que permet l'usage des produits de contraste échographiques avec une focalisation particulière pour l'intensité du rehaussement.

Cette méthode semble présenter une utilité dans la détection de la maladie, dans la quantification de l'activité, dans l'évaluation des complications et dans le suivi du traitement[19-25].

3. **Le CT et l'IRM** sont devenus les examens de première intention dans le diagnostic et le suivi de la maladie de Crohn.

   Ces méthodes sont dépendantes d'une distension intestinale correcte, pouvant être obtenue per os (entérographie) ou par injection automatisée (pompe) via une sonde naso-jéjunale (entéroclyse)[26,27].

   Dans notre pratique, nous avons opté pour la technique per os afin de ne pas irradier complémentairement le patient, quasi systématiquement complétée par la réalisation d'un lavement à l'eau (sans préparation préalable du patient) pour d'une part, ouvrir le colon dans l'idée de réaliser un bilan complet en un seul examen et, d'autre part, de refluer dans le grêle terminal afin de mieux « le distendre » et donc pouvoir l'analyser. Le

produit ingéré par le patient est un mélange de sorbitol (effet osmotique/appel d'eau) et de méthylcellulose (viscosité)[4].

La réplétion est obtenue de manière identique pour le CT ou l'IRM. À la fin de l'imprégnation per os et de façon répétée avant le lavement, elle s'accompagne d'une hypotonie induite (Hyoscin. butylbromid. 20 mg/ml – 2 ampoules par voie IV).

Ces techniques impliquent en outre l'administration d'un produit de contraste intraveineux (iodé au CT, gadoliné en MR).

4. En ce qui concerne **le CT**, bien qu'excellent tant dans le diagnostic que dans le suivi, le principal facteur limitant reste l'irradiation d'une patientèle jeune, dont on ne connait par ailleurs pas l'avenir radiologique, et une discrimination moins précise qu'à l'IRM dans les anomalies pariétales (œdème sous-muqueux). Sa disponibilité et sa rapidité d'acquisition, supérieures à celle de l'IRM, lui gardent une position privilégiée dans le contexte de l'urgence (douleurs abdominales aspécifiques) et dans celui de la recherche de complications aigües, telles qu'occlusions de haut grade, abcès profonds, ainsi que dans le contexte postchirurgical récent.

5. **L'IRM**, qui est au moins équivalente à l'entéro-CT[28, 29] et qui apparaît maintenant comme technique de choix[4, 30-32], dont la sensibilité et la spécificité atteignent 90%[29, 33, 34] tant en ce qui concerne la détection de l'activité que celle des complications, n'a pas toujours connu une fiabilité optimale[35-39].

   L'importante amélioration de la résolution spatiale et en contraste en a fait la technique de référence actuellement[30,40].

   Elle implique la réalisation de séquences en pondérations T1 et T2 dans les plans coronal (principal) et axial (accessoire). Le choix du plan coronal comme référence principale se justifie par sa plus grande rapidité d'acquisition d'images couvrant l'entièreté de la cavité abdominale (très utile pour les séquences avec injection de produit de contraste) et par sa facilité de lecture dans un plan d'abord plus familier aux cliniciens référents (principalement gastroentérologues et chirurgiens abdominaux), favorisant par là même une communication indispensable au suivi des patients.

   En pratique, en accord avec la majorité des auteurs, les séquences suivantes sont le plus souvent employées:

   - T2 bSSFP coronal Fat Sat;
   - T1 3D GE coronal Fat Sat avant contraste;
   - T1 3D GE coronal Fat Sat avec contraste en phase artérielle (30 secondes);
   - T1 3D GE coronal Fat Sat avec contraste en phase portale (70 secondes);

- T2 SS-ETSE coronal sans Fat Sat;
- T2 SS-ETSE axial sans Fat Sat;
- T1 3D GE axial Fat Sat avec contraste en phase tardive (5 à 6 minutes).

Le plan axial, dans lequel les images restent réalisées en phase plus tardive, permet la corrélation dans l'espace de localisations lésionnelles, surtout si elles sont de petite taille, et reste un moyen satisfaisant de comparaison avec les examens antérieurs réalisés dans la modalité CT par exemple.

Sur le plan sémiologique, les paramètres suivants sont analysés qualitativement en routine[33, 34, 41-43]:

- l'épaississement pariétal *(Fig. 5)*;
- le rehaussement pariétal (signe de la cible) *(Fig. 6)*;
- l'œdème sous muqueux (hyperintensité en T2) *(Fig. 7)*;
- la présence de pseudo-polypes;
- la présence de sténose *(Fig. 8)*;
- la présence d'ulcère(s) *(Fig. 9)*;
- la présence de fistule *(Fig. 9, 10)* et d'abcès *(Fig. 11);*
- la présence de ganglions supérieurs ou égaux à un centimètre de petit diamètre et rehaussés au niveau du mésentère adjacent;
- l'aspect du mésentère (signe du peigne) *(Fig. 12)*.

L'analyse porte donc sur les signes d'activité non seulement pariétale, mais également extrapariétale, avec une corrélation significative aux données endoscopiques[18, 44-46]. Cette analyse permet aussi une orientation correcte des patients vers un traitement médical ou chirurgical[47].

La détection des complications (perforantes ou sténosantes) est un des multiples apports de l'IRM[33, 48].

L'injection de contraste selon une technique rigoureuse ouvre la voie à une analyse dynamique du rehaussement[43].

Enfin, l'emploi des séquences de diffusion (DWI) deviendra certainement, dans un futur proche, un appoint important dans la détection de l'inflammation et pourrait peut-être, à terme et sous réserve d'études sur de plus grandes populations, permettre de se passer de l'injection de contraste[49, 50].

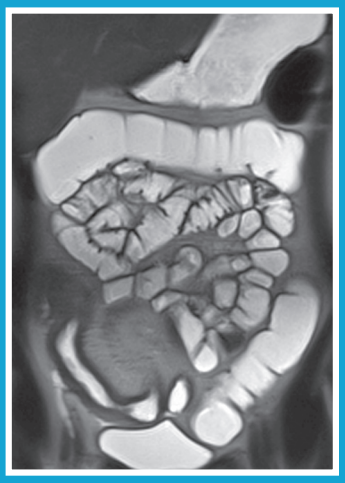


Fig. 5: *Epaississement pariétal.*

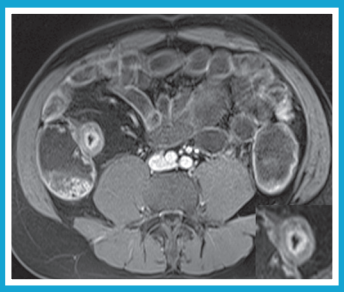


Fig. 6: *Signe de la cible.*

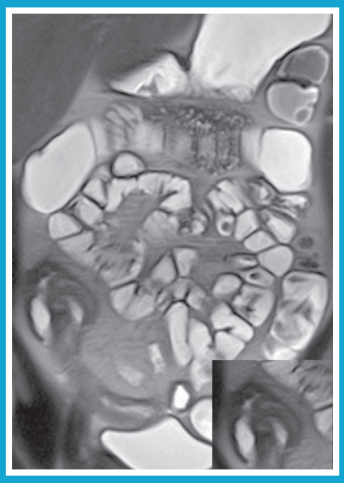


Fig. 7: *Œdème mural T2.*

Fig. 8: *Longue sténose inflammatoire médiogrêle.*

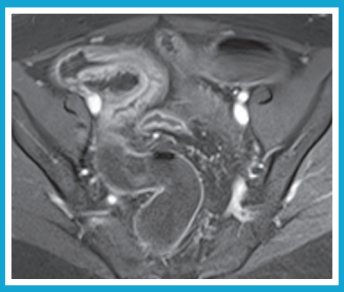


Fig. 9: *Ulcères et fistules murales.*

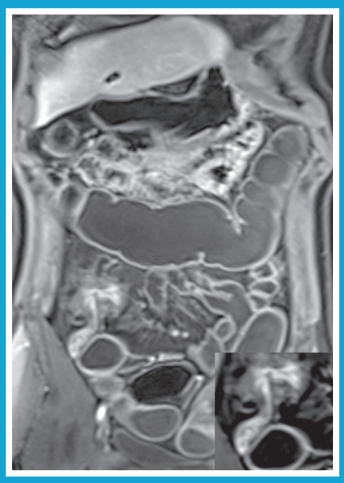


Fig. 10: *Fistule borgne.*

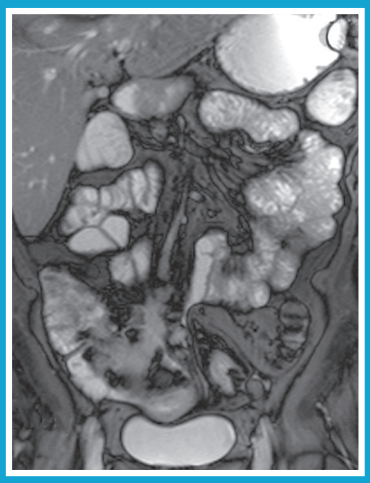


Fig. 11: *Importants remaniements fistuleux et abcédés en regard de l'iléon distal.*

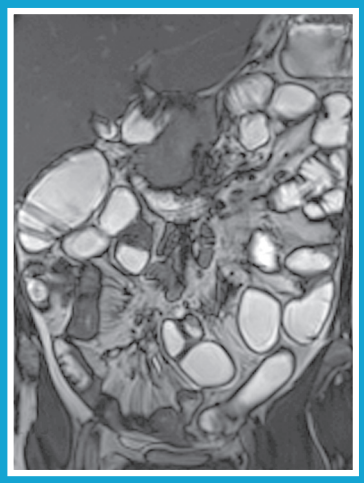


Fig. 12: *Signe du peigne.*

Le potentiel de l'IRM est donc vaste, mais il ne prendra sa pleine expansion que dans un contexte de relations « quasi osmotiques » entre endoscopistes et radiologues pour le meilleur intérêt des patients[51].

6. **Le PET-CT** est également une méthode d'investigation performante[52]. Son caractère irradiant limite toutefois ses indications dans le contexte du suivi de patients majoritairement jeunes. La captation du ^{18}FDG par certains segments en dehors d'une atteinte endoscopique visible reste également à vérifier[53]. Il pourrait être intéressant d'envisager une corrélation à l'IRM.

Ces différentes techniques semblent actuellement répondre aux besoins des patients et des cliniciens dans le bilan initial et dans les bilans de suivi.

Il reste cependant des besoins non rencontrés. C'est dans cet axe de réflexion que s'inscrit ce travail.

La suite de cette introduction passera donc en revue ces besoins non rencontrés et formulera les objectifs de correction et de développement.

Les nouveaux défis de l'évaluation de la maladie de Crohn

1. Activité [34, 42, 54]

Il est désormais établi que l'IRM constitue la méthode de choix dans l'évaluation de l'activité de la maladie de Crohn[28, 29].

Actuellement, on dispose d'un score d'activité MaRIA[34], intégrant 4 éléments sémiologiques différents qui ont montré une excellente corrélation avec l'activité évaluée par endoscopie :

- l'épaississement pariétal;
- le rehaussement pariétal;
- l'œdème sous-muqueux;
- la visualisation d'ulcérations muqueuses.

Par ailleurs, la maladie de Crohn est une atteinte progressive au cours de laquelle le dommage tissulaire s'accumule. Ce dommage apparaît non seulement lors des poussées mais aussi dans les périodes de rémission clinique si le contrôle de la maladie est incomplet.

Dans ce contexte également, l'IRM apparaît aussi comme la technique de choix pour l'identification d'une activité persistante chez des patients cliniquement en rémission.

2. Notion de Rémission profonde[6]

La nécessité de traiter les patients au-delà des symptômes et d'obtenir, au-delà de la rémission clinique, un contrôle biologique de la maladie a comme corollaire qu'il faut pouvoir évaluer objectivement ce contrôle de la maladie. De nombreuses études ont clairement montré la discordance entre l'évaluation clinique des malades, même en utilisant des scores standardisés comme le CDAI, et l'évaluation biologique à l'aide de biomarqueurs ou l'évaluation anatomique à l'aide de l'imagerie[55, 56].

Les marqueurs biologiques les plus utilisés ont été la C-reactive protein (CRP) sanguine et, plus récemment, la calprotectine fécale. Ces marqueurs, imparfaitement corrélés à l'évaluation clinique, peuvent donc révéler une activité persistante de la maladie sous-estimée ou méconnue par la clinique. Toutefois, ces marqueurs sont aussi imparfaitement corrélés à l'imagerie et ne peuvent donc être considérés comme des reflets fidèles des lésions tissulaires persistantes. La calprotectine fécale, globalement mieux corrélée à l'activité endoscopique que la CRP, présente un coefficient de corrélation avec les scores endoscopiques d'activité de l'ordre de 75 à 80%. Le grand avantage des biomarqueurs est leur caractère non invasif et peu coûteux. Ils pourraient donc représenter des outils intermédiaires entre la clinique et l'imagerie aidant à orienter la prise en charge et à sélectionner les patients chez lesquels un recours à l'imagerie endoscopique ou en coupes est indiqué. Nous avons discuté plus haut les avantages et inconvénients respectifs de ces différentes méthodes d'imagerie.

Compte tenu de l'histoire naturelle de la maladie de Crohn, les domaines dans lesquels ces outils objectifs d'évaluation de l'activité et des conséquences de la maladie sont particulièrement utiles sont les suivants : l'évaluation de l'activité inflammatoire tissulaire intestinale d'une part et l'évaluation du dommage tissulaire d'autre part. L'évaluation de l'activité inflammatoire tissulaire intestinale a fait émerger un nouveau concept: celui de la rémission profonde de la maladie. Actuellement, la définition la plus consensuelle de rémission profonde correspond à un stade de rémission associé à un faible risque de progression de la maladie:

- contrôle des symptômes (rémission clinique);
- absence d'évidence biologique d'inflammation[4];
- cicatrisation muqueuse (rémission endoscopique).

Le débat reste actuellement ouvert sur le bénéfice attendu d'une cicatrisation muqueuse complète versus une cicatrisation muqueuse partielle avec un très faible taux résiduel d'activité, sur le besoin éventuel de la documentation d'une cicatrisation transmurale par les examens d'imagerie et sur la valeur ajoutée d'une normalisation des marqueurs biologiques. Des études ultérieures devront clarifier les paramètres les plus pertinents et les seuils à atteindre pour garantir l'absence de progression ultérieure de la maladie.

L'objectif de la rémission profonde étant, au-delà du contrôle symptomatique, l'absence de progression du dommage tissulaire, il apparait important de pouvoir aussi mesurer objectivement ce dommage tissulaire. Sur ce plan, les rhumatologues, évaluant les dommages articulaires des pathologies inflammatoires rhumatologiques, ont été plus précoces et visionnaires que les gastroentérologues. Le score de Sharp dans la polyarthrite rhumatoïde correspond exactement à cet objectif de quantification du dommage tissulaire articulaire cumulé. Une démarche similaire dans la maladie de Crohn pourrait en partie reposer sur l'imagerie en coupes et en particulier l'IRM compte tenu de sa capacité à documenter et quantifier les lésions transmurales destructrices et fibrosantes, consécutives au processus inflammatoire chronique et pouvant par conséquent être retrouvées même lorsque le processus inflammatoire est contrôlé ou s'est éteint.

Une conséquence de cette double notion d'activité de la maladie et de dommage tissulaire est que la définition de la rémission profonde et ses conséquences symptomatiques pourraient être différentes selon qu'on a affaire à une maladie récente ou ancienne.

- En l'absence de dommage tissulaire, la rémission profonde correspond à une résolution d'une ou plusieurs mesures d'inflammation (endoscopie, imagerie, marqueurs) et des symptômes.
- S'il existe un dommage tissulaire, la rémission profonde correspond à une résolution d'une ou plusieurs mesures d'inflammation et à une amélioration des symptômes.

La capacité à mesurer le dommage tissulaire apparait donc importante et complémentaire de celle de la mesure de l'activité inflammatoire dans l'évaluation du malade préalablement au choix ou à l'adaptation de la stratégie thérapeutique. Ces mesures apparaissent également comme essentielles dans l'évaluation de l'efficacité des stratégies thérapeutiques choisies.

Notre travail s'inscrit dans cette perspective d'évaluation: l'ecMR peut-elle, par différents signes aisément visualisables, et si possible quantifiables, contribuer à la définition de la notion de rémission profonde, à la quantification de l'inflammation tissulaire et du dommage tissulaire dans la maladie de Crohn ?

BESOINS NON RENCONTRES ET OBJECTIFS DE NOTRE TRAVAIL

Comme suggéré plus haut, il est important de définir les modalités d'utilisation de l'IRM et les signes sémiologiques les plus pertinents pour contribuer à évaluer tant l'activité de la maladie de Crohn que le dommage tissulaire. Ces travaux sont essentiels à l'utilisation optimale de cet outil dans la prise en charge des patients, en particulier dans le choix et l'évaluation des stratégies de traitement.

Les objectifs de notre travail seront donc de deux ordres:

Généraux: pour répondre aux questions posées ci-avant et plus particulièrement pour tenter d'établir le rôle de l'entero et de l'entero-(colo-)IRM dans la définition de l'activité inflammatoire tissulaire de la maladie de Crohn et dans l'évaluation du dommage tissulaire lié à cette maladie.

Plus spécifiques, ils concernent:

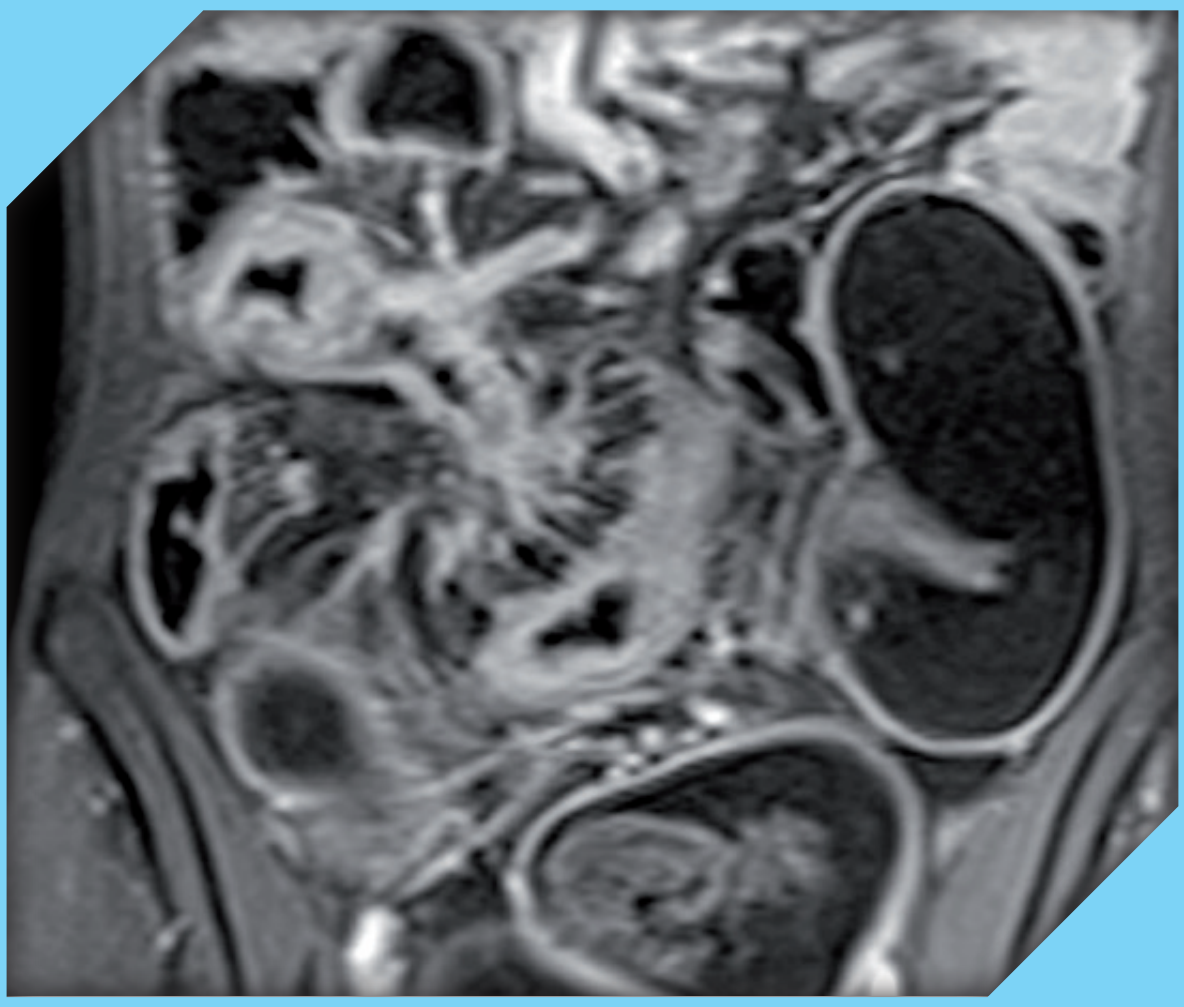
a. l'évaluation des paramètres sémiologiques IRM caractérisant la réponse à un traitement anti-TNF dans la maladie de Crohn *(article 1)*;

b. l'évaluation des paramètres sémiologiques IRM caractérisant au mieux le dommage tissulaire dans la maladie de Crohn *(article 2)*;

c. l'évaluation des paramètres sémiologiques IRM définissant au mieux la rémission profonde de la maladie de Crohn, c'est-à-dire la rémission associée à un faible risque de rechute et/ou de progression *(articles 3 et 4)*.

Article 1

Effects of infliximab therapy on transmural lesions as assessed by magnetic resonance enteroclysis in patients with ileal Crohn's disease



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Effects of infliximab therapy on transmural lesions as assessed by magnetic resonance enteroclysis in patients with ileal Crohn's disease☆,☆☆,★

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KEYWORDS
Crohn's disease;
Imaging;
Complications;
Anti-TNF therapy;
MR enteroclysis

Abstract

Background and aims: Anti TNF therapy induces mucosal healing in patients with Crohn's disease, but the effects on transmural inflammation in the ileum are not well understood. Magnetic resonance-enteroclysis (MRE) offers excellent imaging of transmural and peri-enteric lesions in Crohn's ileitis and we aimed to study its responsiveness to anti TNF therapy.

☆ Gert Van Assche, Karin Herrmann, Alessandra Oortwijn and Thomas Ochsenkühn designed the study. Karin Herrmann developed the MR enteroclysis protocol and performed the site training. Gert Van Assche, Edouard Louis, Simon Everett, Jean-Frédéric Colombel, Jean-François Rahier, Séverine Vermeire, Paul Rutgeerts and Thomas Ochsenkühn recruited patients and contributed to the writing of the manuscript. Dirk Vanbeckevoort, Karin Hermman, Paul Meunier, Damian Tolan, Olivier Ernst reviewed the MR images and contributed to the writing of the manuscript.

☆☆ The corresponding author had full access to all of the data and takes full responsibility for the veracity of the data and statistical analysis.

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Methods: In this multi-center prospective trial, anti TNF naïve patients with ileal Crohn's disease and with increased CRP and contrast enhanced wall thickening received infliximab 5 mg/kg at weeks 0, 2 and 6, and q8 weeks maintenance MRE was performed at baseline, 2 weeks and 6 months and assessed based on a predefined MRE score of severity in ileal Crohn's Disease.

Results: Twenty patients were included; of those, 18 patients underwent MRE at week 2 and 15 patients at weeks 2 and 26 as scheduled. Inflammatory components of the MRE index decreased by ≥2 points and by ≥50% at week 26 (primary endpoint) in 40% and 32% of patients (per protocol and intention to treat analysis, respectively). The MRE index improved in 44% at week 2 and in 80% at week 26. Complete absence of inflammatory lesions was observed in 0/18 at week 2 and 13% (2/15) at week 26. The obstructive elements did not change. Clinical and CRP improvement occurred as early as wk 2, but only CDAI correlated with the MRE index.

Conclusion: Improvement of MRE occurs from 2 weeks after infliximab therapy onwards and correlates with clinical response but normalization of MRE is rare.

INTRODUCTION

The proinflammatory cytokine tumor necrosis factor-alpha (TNFα) plays an important role in the pathogenesis of Crohn's disease, a chronic inflammatory disorder of the gastrointestinal tract. Infliximab, an anti-TNFα monoclonal antibody, binds to TNFα with high affinity, thereby neutralizing its biological activity. The administration of infliximab to patients with moderately-to-severely active CD disease induces and maintains clinical remission and promotes mucosal healing. Mucosal healing with infliximab is associated with a decrease in disease related hospitalizations[1]. However CD is a transmural disease; intestinal wall thickening with fibrosis, muscular hypertrophy and mesenteric hypertrophy with fat accumulation and hypervascularization are characteristic features of CD. The influence of infliximab on transmural CD is unclear. Although initial case reports of intestinal obstruction early after infliximab therapy for ileal CD generated concern about the safety of infliximab in ileal CD with an inflammatory stenosis, a recent analysis of prospective registry data suggests that the risk of obstruction is not specifically increased in infliximab treated patients[2,3]. Transmural imaging with Computed tomography (CT) or magnetic resonance (MR) enterography or enteroclysis provides appropriate assessment of transmural lesions and extramural complications[4]. Magnetic Resonance enteroclysis (MRE) offers unique imaging of the transmural inflammation in intestinal CD and contrast uptake behavior of the diseased bowel wall may allow the discrimination of inflammatory from fibrotic lesions [5–16]. The discriminative power of imaging is however, limited since C is probably never purely fibrostenotic and features

such as contrast enhancement are also influenced by fibrotic changes[15]. Bowel filling via a jejunal tube within the magnet under MR fluoroscopic monitoring also allows for controlled and reliable bowel distension. Recent data with MRE indicate that this technique is very sensitive to detect both inflammatory and fibrotic changes[11].

Therefore, An Open Label, Prospective, Multi-Center trial, on the Effect of the Anti-TNFα Chimeric Monoclonal Antibody Infliximab on Inflammatory and Fibrous Lesions in Patients with Intestinal CD (ACTIF) was designed to assess the impact of infliximab on transmural lesions of CD as visualized by MRE.

PATIENTS AND METHODS

This was an open label, prospective, multi-center pilot trial in patients with documented ileal or ileocolonic Crohn's disease with an indication to start infliximab (Remicade®, Janssen Biotech Inc., Horsham, PA, USA) 5 mg/kg IV induction at weeks 0,2 and 6 and maintenance every 8 weeks thereafter. The indication to start anti TNF therapy for luminal Crohn's disease was based on the European label and patients had moderate to severe active CD failing steroid and/or immunosuppressive therapies. To qualify for the study patients had to be ≥ 18 and ≤ 65 years of age, with a CDAI > 220 and a high sensitivity CRP (hs-CRP) of more than 5 mg/l. Imaging criteria for inclusion were markedly increased Gadolinium (Gd) uptake of the small bowel wall and ileal wall thickening on baseline contrast enhanced MRE. Exclusion criteria were active or latent tuberculosis, contraindications for MRE, treatment with more than 15 mg of systemic corticosteroids (prednisone equivalent) within the 2 weeks prior to baseline MRE, prior bowel resection of > 100 cm or documented abdominal abscess or internal fistula as well as medical contraindications for anti TNF therapy. A standard corticosteroid taper was enforced and all other Crohn's disease therapies were kept stable during the first 26 weeks. Initiation of any medical therapy to treat Crohn's disease was not allowed. After obtaining written informed consent, MRE was scheduled and performed prior to the first infliximab infusion, at weeks 2 and 26. If a MRE had been performed within one month from starting treatment (adhering to the predefined and detailed imaging protocol instructions and without subsequent changes in therapy), the results of this MRE could be used for baseline scoring.

The Crohn's disease activity index, CDAI[17], Harvey-Bradshaw index, HBI[18], the IBD (Inflammatory Bowel Disease) Questionnaire[19], concomitant medications and adverse events were recorded at every visit during the 26-weeks duration of the trial. After the main study of 26 weeks, patients were followed for safety and efficacy of infliximab until 2 years from inclusion.

Contrast enhanced MRE with intraluminal and intravenous contrast application was performed on 1.5 Tesla (T) MR scanners using an identical imaging protocol and imaging parameters at all institutions *(Suppl. Table 1)*. A detailed MRE study manual was developed and

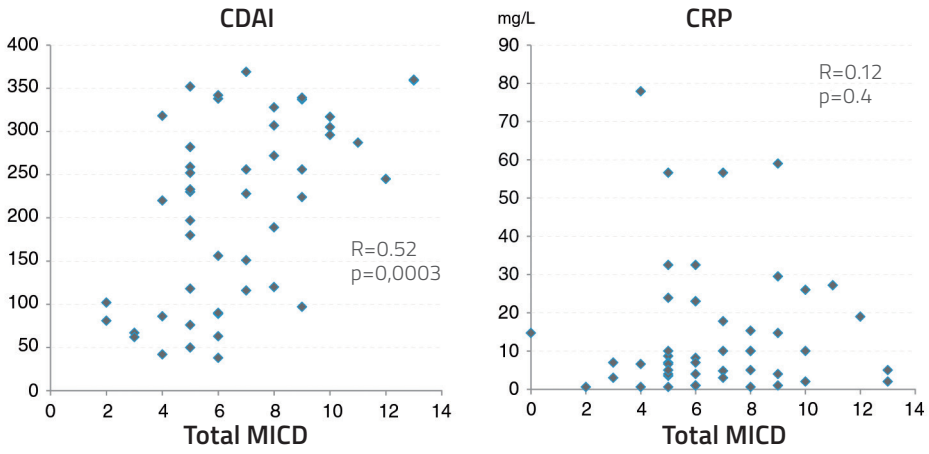

***Fig. 1**: MICD scores correlated with CDAI but not with CRP. The graph represents the data for the total MICD score only. MICD scores, and CDAI and CRP values were pooled at all time points.*

distributed by the Institute of Clinical Radiology, University of Munich, (KAH) including comprehensive instructions for appropriate patient preparation, imaging technique, sequences and imaging parameters. In addition, at least one dedicated abdominal imaging specialist from each participating center received a one-day hands-on training at the training site at University of Munich, prior to initiation of the site. An MRE performed per proctocol in a patient with suspected ileal CD was sent for central review to the training center in Munich (KAH) in order to ascertain appropriate technique and imaging quality and to approve final initiation of the site *(Fig. 1)*.

For MRE all patients underwent placement of a naso-jejunal tube prior to the MRI examination. Final tube position with the tip beyond the ligament of Treitz was confirmed with fluoroscopy. Patients were transferred to the MRI unit and positioned in supine position in the MRI bore. The naso-jejunal tube was connected to an automated infusion pump via an infusion system and 1000–2500 ml of 0.5% methylcellulose solution were applied at a speed of 80–100 ml/min until adequate and homogeneous distention of all small bowel segments was obtained. The filling process was monitored using repetitive SSFSE imaging every 1–2 min during infusion *(HASTE-online; see Table 1)*. Standard protocol imaging was started after completion of the filling phase with SSFSE and SSFP in two planes followed by non enhanced T1w 3D GRE *(See supplementary Table 1).* Prior to non enhanced T1w 3D GRE, spasmolytic agents (Butylscopolamine, Buscopan®, 20– 40 mg, Boehringer Ingelheim, Germany) were administered to control bowel motion. For subsequent contrast enhanced imaging an intravenous contrast agent at standard dose (0.1 mmol/kg/BW; Magnevist®, Bayer Schering, Germany) was injected at 1.5 ml/s and T1w 3D GRE was performed approximately 60 s, 90 s and 180 s post injection. Protocol was completed with T1w 2D GRE imaging *(Supplementary Table 1)*. A newly developed index, MRE score of severity in Ileal Crohn's Disease

(MICD) was used to score CD severity and complications. The MICD was designed to be a combined index of transmural inflammation, extramural involvement and signs of obstructive disease *(Suppl. Fig. 2)*.

The MICD index ranges from 0 to 14 with the inflammatory scores ranging from 0 to 8 and the obstructive scores from 0 to 6. The criteria for scoring lesions associated with transmural ileal CD lesions were based on an extensive review of the recent literature and on a Consensus between Gastroenterologists and Radiologists of this study group.

Scoring included the assessment of the presence and degree of active inflammation as well as the presence and degree of obstruction. Signs of inflammation were determined as increased thickness of the bowel wall, augmented contrast enhancement after intravenous administration of Gd-DTPA and inflammatory reactions beyond the intestinal wall in the adjacent mesenteric tissue as a sign of extramural disease. Measurements of the small bowel wall thickness were performed on T2w weighed and SSFP images at three different levels of the inflamed bowel segment where wall thickening was subjectively deemed as maximal. As in contrast enhanced studies the depiction of the wall dimensions depends heavily on the uptake pattern, these are less reliable for the exact delineation of the bowel wall. Distance measurements were placed in cross sectional images where the small bowel was perpendicular to the imaging plane. Of the three measurements in each sequence the median was calculated as a basis for the scoring. Zoom function was allowed to facilitate a more precise placement of measurements. In order to assess the contrast enhancement of the bowel wall, first, "normal" bowel wall enhancement was determined for reference. Hereto, regions of interest (ROI) for signal intensity (SI) were placed in one location of normal bowel and subsequently in three different locations of diseased bowel and in both the unenhanced and enhanced T1w images to calculate the relative uptake in percentages. The obstructive component was assessed by measuring the minimal diameter of the bowel lumen over all sequences in a cross sectional plane strictly perpendicular to long axis of the bowel and the degree of prestenotic dilatation upstream to the diseased bowel segment. Prestenotic dilatation was semi-quantified taking the maximum diameter of dilatation and comparing it to the luminal distension of unaffected bowel of the same anatomic region.

At the end of the trial all MRE images were de-identified as for patient ID, patient number, date of assessment or visit number and distributed among several radiologists for review and scoring (KAH, DT, DV, PM). After all MRE had been read, the scores were unblinded and correlated to clinical outcomes.

The study protocol was approved by the Institutional Review Boards of all participating centers.

ENDPOINTS AND STATISTICAL CONSIDERATIONS

The primary endpoint of this study was the number of patients achieving a clinically significant change in the MICD score defined as an overall improvement of at least 2 points and an improvement of at least 50% in the inflammatory subscores (range 0–8) at wk 26. For the primary endpoint we focused on a minimal 50% improvement of the inflammatory subscores as we assumed they would best respond to an anti-inflammatory treatment. Secondary endpoints included change in MICD total and individual scores over time, the number of patients with clinical improvement and CDAI remission (< 150), the correlation between MICD scores and CRP and CDAI respectively and the safety of infliximab in this population particularly pertaining to intestinal stenosis and resections. Non-parametric tests were used to analyze changes in continuous variables and Spearman's rank statistics were used to test for correlations.

Both an intention-to-treat (ITT) and per protocol analysis were planned in the assessment of primary and secondary efficacy endpoints and for safety outcomes. The ITT population included all patients who received one or more IFX infusions and did not violate the inclusion criteria. The perprotocol population included all ITT patients where an MICD score was available at weeks 0, 2 and 26 and IFX dosing had not been interrupted prior to wk 26.

Last Observation Carried Forward (LOCF) with non-responder imputation, was used in the ITT analysis. This means that patients with missing MRE data were considered to be non-responders for the primary endpoint at wk 26. We performed no formal power calculations, since this was a pilot trial and no literature data on the response of transmural lesions to anti TNF therapy were available when this study was designed.

Table 1: Baseline characteristics of the patients.

	N=20
Male/female	7/13
Age (median, range)	29 (19–54)
Disease duration (median, years)	4.8 (0.3–21.0)
CDAI	277 (245–317)
CRP (mg/l)	15.3 (6.0–25.0)
HBI	9.0 (7.3–10.0)
Weight (kg)	65 (57–80)
MICD	7 (5–9)
Concomitant medications	Aza/6-MP: 11/20 Systemic steroids: 4/20 Budesonide: 7/20 5-ASA: 3/20

Note: *All patients in the safety population (n=20) were included. Data are median and numbers in parentheses indicate range.*

RESULTS

Patient enrollment

From July 2007 until September 2010, 20 patients (13 women and 7 men, median age 29 (19–54), median disease duration 4.8 years (0.3–21.0))

were enrolled in the study at the different sites and formed the study population. Patient characteristics are summarized in *Table 1*. One patient was excluded because of a major protocol violation (normal CRP at entry, ITT : n = 19) and 15 patients fulfilled all criteria for the per protocol analysis *(Suppl. Fig. 2)*.

MRE response

A decrease in MICD index with at least 2 points or more and an improvement with at least 50% in the inflammatory subscores on the wk 26 MICD score (primary endpoint) was reached by 40% (6/15) of patients per protocol and 32% (6/19, ITT analysis) respectively. The median total MICD scores improved at week 26 compared to baseline [wk 26: 5 (IQR: 3–6.8), wk 0: 7 (5–9), pb 0.03] as did the inflammatory sub-scores [wk 26: 3 (IQR: 0.25–4), wk 0: 4 (3–6), p< 0.03] *(Figs. 2 and 3)*. In contrast, the obstructive disease sub-scores were similar at the different time points *(Table 2)*. Absence of inflammatory lesions (as defined by a score of 0 in the inflammatory sub-scores of the MICD index) occurred in none of the patients at wk 0 and in 2/15 patients at wk 26. Worsening of the scores with a maximum of 1 point was observed in one patient for the inflammatory scores and in one patient for the obstructive disease scores (data not shown).

Clinical outcomes and correlation with MRE response

The median CDAI, median HBI and hs-CRP improved as early as week 2 *(Table 2)*. At week 2, 8/19 patients had achieved CDAI remission (< 150) and 6/19 HBI remission (< 4); at wk 26 remission rates were 6/19 for CDAI and 7/19 for HBI. C-reactive protein levels dropped

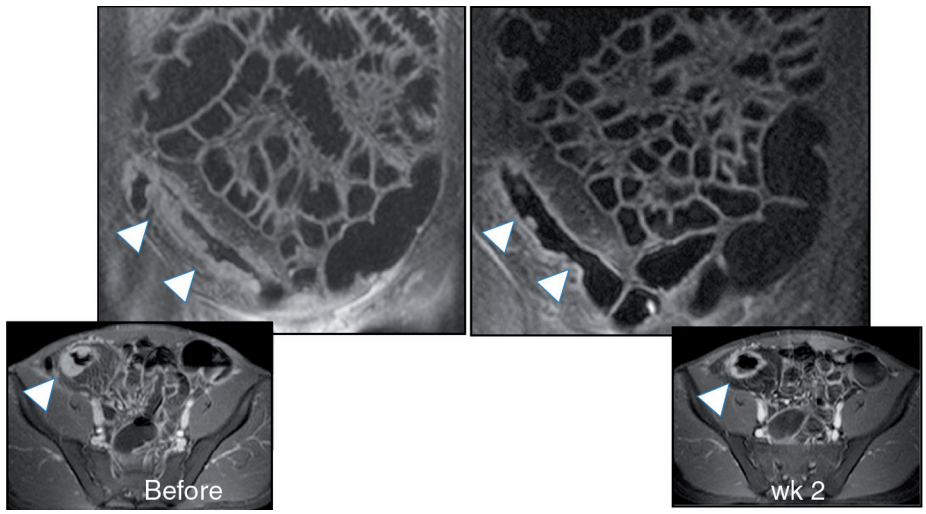

***Fig. 2**: Representative images of the evolution of the MRE before and 2 weeks after infliximab 5 mg/kg IV. Coronal and transverse sections of the same patient are depicted. Arrows focus on the ileal segment that was selected for assessment.*

by at least 50% compared to baseline in 14/18 patients at wk 2 and in 8/15 at wk 26. The individual MICD total scores and inflammatory sub-scores correlated with the CDAI values ($p < 0.001$ and $p < 0.01$), but not with CRP. *(Table 3; Fig. 1)*. A numerical but non-significant increase in IBDQ was observed over time *(Table 2)*. The median weight was unaffected by treatment and the median change in weight was + 1.4 (0–4) kg.

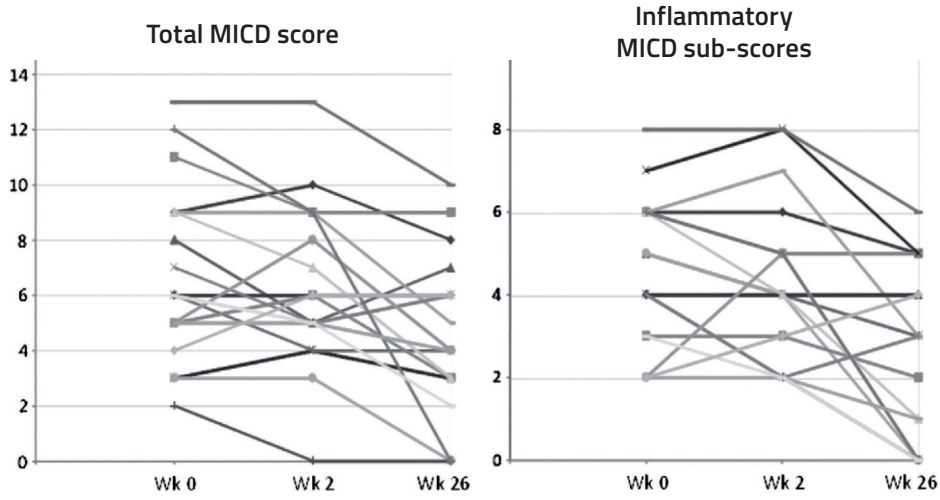

***Fig. 3**: Change of the inflammatory components of the MICD and of the total score in individual patients.*

Table 2 : Clinical and MRE outcomes after treatment.

	Wk 0 (n=19) median, IQR	**Wk 2**	***Wk 26***
Total MICD score	7.0 (5.0–9.0)	6.5 (6.5–8.8)	5.0 (3.0–6.8)*
Inflammation subscores	4.0 (3.0–6.0)	4.0 (3.0–5.5)	3.0 (0.25–4.0) *
Obstructive subscores	3.0 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (2.0–3.0)
CDAI	277 (249–338)	169 (109–269)*	126 (67–180) *
CRP (mg/l)	15.3 (6.0–25.0)	3.0 (1.8–5.6)*	6.6 (5.5–12.3)
HBI	9.0 (7.3–10.0)	5.0 (3.3–9.3)*	4 (2.0–6.0)**
IBDQ	138 (113–162)	157 (131–168)	171 (139–191)
Weight (kg)	65 (57–80)	65 (59–82)	69 (59–81)

***Note:** all patients in the ITT population (n=19) were included.*

**p<0.05 , **p<0.01*

Safety

Through week 26 five serious adverse events were reported in 5 patients and these were judged to be possibly related to infliximab therapy. Three patients had discontinued infliximab by wk 26 due to pregnancy (n = 1), an infusion reaction (n = 1) and pancreatitis (n = 1, concomitant azathioprine) *(Suppl. Table 2)*.

Table 3 : Correlation of MICD with CRP and CDAI.

	CDAI	CRP
Total MICD	R=0.52 (p=0.0003)	R=0.12 (p=0.4)
Inflammation subscores	R=0.45 (p<0.01)	R=0.13 (p=0.4)

Note: *Spearman Rank statistics were used to test for potential correlation between all paired data at different timepoints..*

No CD related surgeries were needed until wk 26, although one patient experienced a pyloric stenosis that was endoscopically dilated. Beyond wk 26 until the end of the two year follow up two more ileo-colonic symptomatic stenoses were observed but none of the patients required surgery. Seven more patients stopped infliximab beyond wk 26, mainly due to side effects (infusion related reactions n= 4, skin lesions n= 1, loss of response n= 2). There were no serious adverse events related to the MRE.

DISCUSSION

The effect of infliximab and other anti TNF agents on mucosal lesions has been well studied, but the impact of anti TNF agents and medical treatment in general on transmural and mesenteric lesions is less clear. We here provide the first prospective evidence that the anti TNF agent infliximab induces rapid improvement of transmural inflammation assessed by MRE in an open label prospective study. Interestingly, complete resolution of lesions was a rare phenomenon and the vast majority of patients had persistent signs of inflammation and signs of obstruction at imaging did not change with infliximab therapy for 26 weeks. Since inflammation leads to fibrostenosis in Crohn's disease[20,21], one can speculate that earlier introduction of thiopurines and anti TNF therapies may prevent damage of the affected bowel segments.

Recently, results of a retrospective analysis of a cohort of patients treated with infliximab for Crohn's disease and followed with CT enterography at the Mayo Clinic indicated that signs of active Crohn's disease such as wall thickening and contrast enhancement, but more importantly signs of mesenteric inflammation (comb sign) improved in more than 60% of patients with treatment. The authors suggested that they had underestimated the beneficial effects of the anti TNF therapy since repeated CT had been performed only in patients with ongoing symptoms. We however, confirm with a prospective trial that even in patients

with a clear clinical response to infliximab therapy, persistence of transmural abnormality is common using MRE. Pre-existing bowel damage due to longstanding inflammation and subsequent fibrostenosis most likely contributes to the fact that in our study the sub-scores aimed at assessing obstructive disease were least improved by anti TNF therapy. However, some signs of inflammation such as contrast enhancement and extramural involvement persisted in the majority of patients and a complete resolution of lesions was not observed. It is possible that more delayed MRE imaging beyond wk 26 after the start of infliximab therapy would have demonstrated additional improvement in MICD scores, but this was not assessed. Therefore, data in a larger set of patients with a long term follow up are needed to study the clinical relevance of evaluating signs of obstructive disease on MRE. The impact of persistent lesions on long term outcomes also deserves future exploration. However, it is important to note that, albeit we only followed 19 patients out to 2 years after start of infliximab, no surgeries for obstructive disease were needed.

We opted for enteroclysis in this study since this technique is considered to provide better distension of small bowel loops and assessment of stenotic disease than standard enterography. However, recent evidence suggests the adequate filling can be obtained with MR enterography[11,12]. We also chose to design a novel MRE based score to quantify the results of our assessments. Based on the available literature at the time of study initiation and clinical experience, items such as wall thickening, increased contrast enhancement, extramural involvement and pre-stenotic dilation were selected and prioritized. Although one strong indicator (submucosal edema with increased signal intensity in T2 weighted imaging) was not included in our score, all other signs have been validated in the literature in the meantime and were confirmed as strongly indicative of active inflammatory disease[10–12,14].

Although we opted for a primary endpoint at six months, a second MRE was performed as early as 2 weeks after the initiation of treatment, since infliximab induces early clinical improvement in patients with luminal Crohn's disease[22]. Although some degree of improvement in transmural inflammation was observed at week 2, clinical (CDAI and HBI) and CRP improvement was more pronounced at this early time point. We hypothesize that a rapid improvement of mucosal rather than transmural inflammation drives the early change in symptoms and in CRP. However, earlier data with CT enterography have indicated that persistent serosal and extraintestinal inflammation was associated with an increased CRP[23]. In this study, we observed a poor correlation with CRP in general.

Our study has several limitations. This was a pilot trial in a limited number of patients. Since this study is the first prospective trial on the early and medium term responsiveness of MRE to medical therapy in ileal Crohn's disease and since we opted for an open label strategy with infliximab, formal power calculation were not feasible. Our results should therefore be interepreted with caution. Patients were not consented to a baseline ileoscopy and therefore we are unable to correlate the MRE finding with mucosal lesions. We used a novel MRE based activity

score for ileal Crohn's disease that has not been externally validated. However, the results of our study indicate that the MICD index is sensitive to change over time. We also found a moderate correlation with clinical activity assessed by CDAI but not with CRP. In the Mayo cohort study concordance between CT enterography response and clinical improvement was poor, but clinical outcomes were not fully quantified[13]. Since 2006 more data on the use of MRI to assess ileocolonic Crohn's disease have become available[10–12] and a 'segment based' quantitative score applicable to the terminal ileum and the colon has been validated[10,11]. Most of this evidence was obtained with MR enterography, but the criteria proposed in the cohort studies and in the validated MaRIA score[10,11] correspond well with our MICD score. We were unable to change the primary outcome of our study after it had been initiated in 2007, but further cross validation of the different MRI based activity scores is needed.

Although it was an open label study, MRE evaluations were carefully and adequately blinded and we observed a correlation between clinical activity and the MICD. In addition, whilst there were a limited number of participants, this was intended as a pilot observational study. Finally, the broad range of disease duration (Median 4.8 years, range 0.3–21 years) in this study group may have biased towards a poor response.

We selected patients with active inflammation based on the presence of an increased CRP and a marked increase in contrast uptake by the ileal wall. Patients with evidence of abdominal sepsis (abdominal abscess) were excluded since anti TNF therapy would be contraindicated. The selection of patients based on signs of active transmural inflammation stemmed from the theoretical concern that anti TNF therapy could precipitate surgery in patients with an ileal stenosis. However recent data have confirmed that patients with an increased baseline CRP respond better to infliximab therapy[24,25] and in the selected population entered in our trial, no intestinal surgery was needed until 6 months after the start of infliximab therapy despite the presence of ileal wall thickening and some luminal dilation in all patients (though one patient developed a symptomatic pyloric stenosis that was successfully dilated). Finally, our sample size was too small to allow for a proper identification of predictors of response based on cross sectional imaging and further larger studies are awaited.

In summary, infliximab induces improvement of transmural and extraintestinal inflammatory lesions in ileal Crohn's disease assessed by MRE but signs of inflammation and obstruction persist despite clinical remission. More prospective, controlled studies are needed to better define the role of transmural imaging to evaluate the efficacy of new therapeutic agents and to delineate the clinical consequences of transmural healing or persistence of inflammatory lesions.

CONFLICTS OF INTEREST

Gert Van Assche, Thomas Ochsenkühn, Edouard Louis, Jean-Frédéric Colombel, Simon Everett, Paul Rutgeerts and Séverine Vermeire served as consultants for or received speakers fees from Schering–Plough, a subsidiary of Merck & Co, Inc. or Centocor Research & Development, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC.

Jean-François Rahier received Research Support from Schering–Plough, a subsidiary of Merck & Co.

Dirk Vanbeckevoort, Isolde Aerden, Olivier Ernst, Karin Herrmann, Paul Meunier and Damian Tolan have no conflicts of interest to declare.

Alessandra Oortwijn is an employee of Centocor Research & Development, a division of Johnson & Johnson Pharmaceutical Research & Development, LLC.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2013.01.011.

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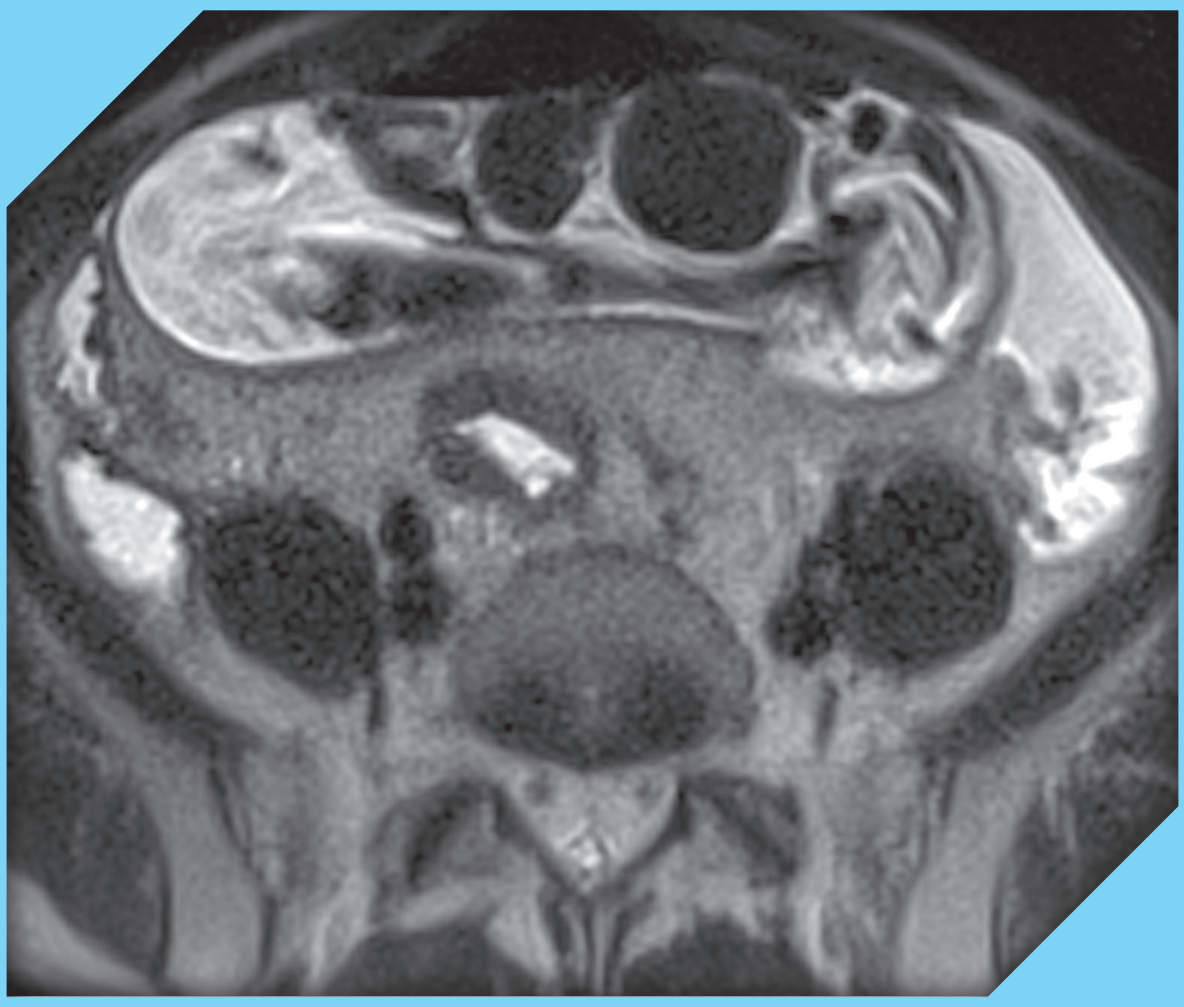
Article 2

Development of the Lemann index to assess digestive tract damage in patients with Crohn's disease



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CLINICAL—ALIMENTARY TRACT

Development of the Lémann Index to Assess Digestive Tract Damage in Patients With Crohn's Disease

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See Covering the Cover synopsis on page 1; see editorial on page 8.

BACKGROUND & AIMS: There is a need for a scoring system that provides a comprehensive assessment of structural bowel damage, including stricturing lesions, penetrating lesions, and surgical resection, for measuring disease progression. We developed the Lémann Index and assessed its ability to measure cumulative structural bowel damage in patients with Crohn's disease (CD). **METHODS:** We performed a prospective, multicenter, international, cross-sectional study of patients with CD evaluated at 24 centers in 15 countries. Inclusions were stratified based on CD location and duration. All patients underwent clinical examination and abdominal magnetic resonance imaging analyses. Upper endoscopy, colonoscopy, and pelvic magnetic resonance imaging analyses were performed according to suspected disease locations. The digestive tract was divided into 4 organs and subsequently into segments. For each segment, investigators collected information on previous operations, predefined strictures, and/or penetrating lesions of maximal severity (grades 1–3), and then provided damage evaluations ranging from 0.0 (no lesion) to 10.0 (complete resection). Overall level of organ damage was calculated from the average of segmental damage. Investigators provided a global damage evaluation (from 0.0 to 10.0) using calculated organ damage evaluations. Predicted organ indexes and Lémann Index were constructed using a multiple linear mixed model, showing the best fit with investigator organ and global damage evaluations, respectively. An internal cross-validation was performed using bootstrap methods. **RESULTS:** Data from 138 patients (24, 115, 92, and 59 with upper tract, small bowel, colon/rectum, and anus CD location, respectively) were analyzed. According to validation, the unbiased correlation coefficients between predicted indexes and investigator damage evaluations were 0.85, 0.98, 0.90, 0.82 for upper tract, small bowel, colon/rectum, anus, respectively, and 0.84 overall. **CONCLUSIONS:** In a cross-sectional study, we assessed the ability of the Lémann Index to measure cumulative structural bowel damage in patients with CD. Provided further successful validation and good sensitivity to change, the index should be used to evaluate progression of CD and efficacy of treatment.

Keywords: Illness Index Severity; MRI; Response to Therapy; Prognosis.

Crohn's disease (CD) is a chronic inflammatory disorder of the bowel that is characterized by periods of clinical remission alternating with periods of recurrence. Persistent inflammation is believed to lead to progressive

Abbreviations used in this paper: **CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CT, computed tomography; DVD, digital versatile disc; ICC, intraclass correlation coefficient; IPNIC, International Program to develop New Indexes in Crohn's disease; IQR, interquartile range; MRI, magnetic resonance imaging.**

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bowel damage that, over time, will manifest in the development of strictures, fistulae, and abscesses[1–3]. These complications frequently lead to loss of function and need for surgical resection, which, in turn, can lead to disability[4]. As in other chronic inflammatory diseases, such as rheumatoid arthritis, the treatment paradigm in CD is currently shifting from mere symptom control toward the reduction of long-term disease sequelae.

Several clinical and endoscopic indices are currently used both in clinical trials and clinical practice to measure the severity of CD and its impact on quality of life[5]. These indices only measure disease activity at a specific time point. The consequences of long-term progression of disease are mainly assessed by the rate of surgical resections, hospitalizations, and mortality[6]. Therefore, a new instrument is needed to measure the cumulative structural bowel damage caused by CD over time, and to assess the impact of new treatment strategies on long-term outcomes.

The main principles that should be used for measuring bowel damage in CD have been described previously[7]. There is a need for a scoring system based on a comprehensive assessment of structural bowel damage, including stricturing lesions, penetrating lesions (fistulae and abscesses), and surgical resection. It should be a measure of disease progression ranging from a minimal value corresponding to absence of damage to a maximal theoretical value corresponding to the complete resection of the digestive tract[7].

Here, we report the development and the first validation of the Lémann Index, the first global CD damage index assessing cumulative structural bowel damage in CD.

METHODS

The study was run by the International Program to Develop New Indexes in Crohn's Disease (IPNIC) group, which is an international working group including 28 gastroenterologists from 15 countries, 1 surgeon, 2 radiologists, and 1 biostatistician.

Study Design

This prospective, multicenter, international, cross-sectional, observational study was initiated in August 2008. Institutional Review Boards and independent ethics committees of the participating institutions approved the protocol when required by national rules. Informed consent was obtained from all the participating patients according to national guidelines.

A total of 24 centers in 15 countries were involved in data collection. Investigators from each center were asked to recruit a set of 10 CD patients. Inclusions were stratified within each set by known or suspected disease location (upper gastrointestinal tract, small bowel, colon and/or rectum, and anus) and disease duration (<2 years, ≥2 years and <10 years, and

≥10 years) at the time of enrollment as follows: 1 patient with at least upper gastrointestinal tract involvement, 3 patients with at least small bowel involvement, 3 patients with at least colon and/or rectum involvement, and 3 patients with at least anal involvement, with 1 patient with each disease duration for the latter 3 involvements. The centers that quickly enrolled a first set of 10 patients were allowed to enroll a second set of 10 patients using the same criteria.

Inclusion criteria were age older than 16 years and confirmed diagnosis of CD > 3 months before enrollment. Exclusion criteria were female patients with known or suspected pregnancy, or without effective contraception, and patients with glomerular filtration rate of <30 mL/min.

At enrollment, complete medical information, including history of previous surgery and physical examination, was obtained. According to the investigational protocol, abdominal-magnetic resonance imaging (MRI) was performed in all patients. Abdominopelvic computed tomography (CT) was performed at the investigator's discretion. Further investigations were based on the disease location: upper endoscopy for upper digestive tract, colonoscopy for colorectal disease, and pelvic MRI for perianal disease. In each center and for all patients, investigations were performed using usual center conditions.

For each patient, the study lasted a maximum of 4 months, with all visits (enrollment and subsequent investigations) occurring within 120 days.

Identification of Damage Components

For the purposes of the analysis and the creation of the Lémann Index, the digestive tract was divided into 4 organs: upper digestive tract, small bowel, colon/rectum, and anus. Each organ was further divided into segments: 3 segments for the upper digestive tract (esophagus, stomach, and duodenum), 6 for the colon/rectum (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum), and 1 for the anus. For small bowel, each lesion within 20-cm length was considered to represent one small bowel segment, and the number of segments was capped at 20.

For each organ, surgical procedures were defined in the protocol by grade of severity on an ordinal scale ranging from 0 (none) to 3 (resection) and stricturing and penetrating lesions were defined and illustrated in the protocol by grade of severity on an ordinal scale ranging from 0 (none) to 3 (maximal) per investigational method *(Table 1 and Supplementary Material, illustrations for small bowel)*.

The most severe surgical procedure at each segment was assessed based on medical history. Stricturing and penetrating lesions of maximal severity were assessed at each segment

with each appropriate imaging technique, for example, for stomach, stricturing and/or penetrating lesions were determined separately at each examination, MRI, CT scan if available, and upper endoscopy (eg, a stricturing lesion of grade 1 at MRI, a stricturing lesion of grade 2 at upper endoscopy, and a stricturing lesion of grade 1 at CT could be observed).

Organ Damage Evaluation

The initial strategy was to ask investigators (1 gastroenterologist and 1 radiologist working in pairs within each center) to globally evaluate damage at each of the 4 organs on a range of 0 (no damage at all) to 10 (total resection of the organ), by integrating all components of damage caused by CD to all segments of the organs (ie, for each segment, surgical procedure of maximal severity and stricturing and penetrating lesions of maximal severity for each investigational method; for further details, please see Supplementary Material, Methods section). Due to inconsistent results obtained with the initial strategy, a second strategy was attempted in which surgical interventions other than surgical resections and major surgery leading to substantial anal sphincter damage were not taken into account to estimate segmental damage evaluation and damage evaluation was assessed separately at the segmental level. For each segment, investigators assessed a damage evaluation ranging from 0.0 (no damage) to 10.0 (maximal damage equivalent to a complete resection), taking into account the presence and length (≤ 5 cm or >5 cm) of stricturing lesions of maximal grade of severity, and/or the presence of penetrating lesions of maximal grade of severity, as assessed with each appropriate technique (for further details, please see Supplementary Material, Methods section).

For each organ, a cumulative damage evaluation was then calculated as the sum of the segmental damage evaluations provided by the investigators plus the damage attributed to resected segments in case of previous total resection (10.0 for each segment), taking into account the individual relative weights attributed by the investigator to each segment within the organ (for relative weights and in case of partial resection, please see Supplementary Material, Methods section). The 4 calculated organ damage evaluations were then standardized to a scale of 0.0 to 10.0 according to the total number of segments per organ.

Global Digestive Tract Damage Evaluation

Investigators were asked to derive from the 4 calculated organ damage evaluations a global damage evaluation ranging from 0.0 (no damage) to 10.0 (theoretical maximum value corresponding to complete resection of the whole digestive tract), taking into account the relative importance they gave to each organ in terms of damage.

Table 1: Severity Scale for Damage Lesions (Stricturing Lesions, Penetrating Lesions), and History of Surgical Interventions Per Organ and Segment and for Each Investigational Method

Organ	Investigational method	n*	Segment	Grade 1	Grade 2	Grade 3
Surgical interventions Upper tract		3	Esophagus Stomach Duodenum	-	Bypass diversion or strictureplasty	Resection
Small bowel		20	Each 20-cm segment	-	Bypass diversion or strictureplasty	Resection
Colon/Rectum		6	Each segment	-	Stomy, bypass diversion or strictu-replasty	Resection
Anus		1	Anus	Reconstruction procedure, flap, coring out fistula track or laying open of fistula	Major surgery lea-ding to substantial sphincter damage** Temporary diver-sion	Definitive diversion Proctectomy
Stricturing lesions Upper tract	Endoscopy	3	Esophagus Stomach Duodenum	-	Lumen narrowing, passable	Stricture, nonpassable
	MRI or CT	2	Stomach Duodenum	Wall thickening <3 mm or segmen-tal enhancement without prestenotic dilatation	Wall thickening ≥3 mm or mural stratification without prestenotic dilatation	Stricture with prestenotic dilatation
Small bowel	MRI or CT	20	Each 20-cm segment	Wall thickening <3 mm or segmen-tal enhancement without prestenotic dilatation	Wall thickening ≥3 mm or mural stratification without prestenotic dilatation	Stricture with prestenotic dilatation
Colon/Rectum	Colonoscopy	6	Each segment		Lumen narrowing, passable	Stricture, non passable
	MRI or CT	6	Each segment	Wall thickening <3 mm or segmen-tal enhancement without prestenotic dilatation	Wall thickening ≥ 3 mm or mu-ral stratification without prestenotic dilatation or <50% of the lumen	Stricture with pres-tenotic dilatation or >50% of the lumen
Anus	Clinical examination	1	Anus	Mild stricture	Frank stricture, passable	Frank stricture, nonpassable
Penetrating lesions Upper tract	Endoscopy	3	Esophagus Stomach Duodenum	Superficial ulceration	Deep ulceration	Fistula
	MRI or CT	2	Stomach Duodenum	-	Deep transmural ulceration	Phlegmon or any type of fistula
Small bowel	MRI or CT	20	One 20-cm segment	-	Deep transmural ulceration	Phlegmon or any type of fistula
Colon/rectum	Colonoscopy	6	Each segment	Superficial ulceration	Deep ulceration	Fistula
	MRI or CT	6	Each segment	-	Transmural ulceration	Phlegmon or any type of fistula
Anus	Clinical examination	1	Anus	Anal ulceration	Multiple fistulae	Multiple fistulae with extensive anal and perianal tissue destruction
	MRI or CT***	1	Anus	Simple fistula****	Branching fistula, multiple fistulae, or any type of abscess >1 cm	Extensive anal and perianal suppu-ration, horseshoe abscess, or fistula(e) involving or exten-ding above the levator plate

** Number of segments.*
*** Division of the internal anal sphincter, external anal sphincter, or both for half or more of the length of the anal canal.*
**** Only in case of abnormality at clinical examination.*
***** Fistula extending from the anal canal to the perianal skin, but involving only the lowermost, or none, of the anal sphincter muscles, and without any secondary tracks).*

Data Collection

At each study center, investigators prospectively collected the patient's data at enrollment using an anonymous electronic case report form.

The enrollment form of the electronic case report form included birth date, sex, height, weight, date of CD diagnosis, date of enrollment, known and suspected CD locations at the time of enrollment, CD activity assessed by the Crohn's Disease Activity Index (CDAI)[8], and calculated creatinine clearance. History of surgical procedures, including resection with the percentage of resected segment (in case of partial resection), was collected for all segments of the 4 organs in the surgical procedure form. Stricturing lesions of maximal grade of severity (with length ≤ 5 cm or > 5 cm) and penetrating lesions of maximal grade of severity were recorded per segment using one form for each imaging technique. Newly recorded information was automatically transferred to the organ damage evaluation form, allowing investigators to record their estimates of segmental damage evaluations, and then the 4 organ damage evaluations were calculated as described. Finally, the 4 calculated organ damage evaluations were automatically transferred to the global damage form, allowing investigators to record their global damage evaluation estimate.

Design of the Inter-Observer Variation Study of Organ and Global Indexes

An inter-observer variation study of organ and global indexes according to stricturing and penetrating lesions per grade was performed using MRI data. It was restricted to 6 centers (1 gastroenterologist and 1 radiologist per center).

To summarize, digital versatile disc (DVD) recordings of MRI examinations were selected from those 6 centers in successive blocks, 6 for upper tract lesions and 20 for anus, colon/ rectum, and small bowel lesions (for the selection of centers and of MRI examinations, please see Supplementary Material, Methods section). For each block, a balanced incomplete block design, giving the same weight to each center within each block in the inter-observer variation study, was used to determine readings in each center. DVDs were read by the radiologist and gastroenterologist pair within each center. Each read 5 DVDs within the upper tract location block and 10 DVDs within each block corresponding to the 3 other locations. Each DVD of the upper tract block was read by 5 pairs and each DVD of the blocks of the other organs was read by 3 pairs.

Data collection followed the same scheme, but was restricted to lesions at abdominal MRI and at pelvic MRI, when available. No segment or organ damage evaluations were performed.

Statistical Analyses

For patient and disease characteristics at enrollment, distributions were described through sample size, frequency, and percentage or median and interquartile range (IQR) on the whole sample.

For the index construction, each predicted organ index was constructed through a multiple linear mixed model in the organ subsample composed of all patients with organ damage known or suspected at enrollment and all patients with organ damage found during investigations (when organ damage was unknown and unsuspected at enrollment)[9]. Because lesions of grade 3 in the upper tract were scarce, 3 patients from 2 centers with lesions of grade 1 or 2 were replaced by 3 patients from the same centers with lesions of higher severity grade. In this model, the dependent variable was the calculated organ damage evaluation (ie, the sum of the investigator segmental damage evaluations taking into account lesions only, and using median segmental weights across investigators. For further details, please see Supplementary Material, Methods section). The independent variables of the model were the numbers of segments with stricturing lesions, regardless of their length, of each severity grade, the number of stricturing lesions with length >5 cm of each severity grade, and the number of segments with penetrating lesions of each severity grade. In addition, an independent variable (the investigator) was included as a random factor to take into account the dependence between estimates performed by the same investigator on different patients. This random factor was not used to construct the upper tract index because most (8 of 12) of the investigators had included only 1 patient with upper tract lesions. The multiple linear mixed model allowed estimation of the linear combination of independent variables, as well as the random factor variance, through restricted maximum likelihood. The independent variables were selected manually using backward selection and likelihood ratio test. The final coefficients of the organ damage index were derived from the estimated coefficients rounded to the nearest 0.5.

The same method was used to construct the predicted global index using investigator global damage evaluation as the dependent variable, the 4 calculated organ damage evaluations as independent variables, and the investigator as an independent random factor. The final coefficients of the Lémann Index were derived from the global index estimated coefficients multiplied by 10 and rounded to the nearest unity.

The quality of the predicted organ and global indexes was assessed as follows:

- The proportion of the variance of the dependent variable explained by the multiple linear mixed model was estimated as proposed by Xu from the H_0 model using only random factors (for more details, see Supplementary Material, Methods section)[10].

- The scatterplot of the standardized residuals (difference between predicted organ or global index and the calculated organ or global damage evaluation divided by its SD) as a function of the organ or global index, predicted through the multiple linear mixed model: The residuals should follow a Gaussian distribution, centered on 0, with variance independent of the organ or global index, with a limited number of high values (2.5% positive higher than 1.96 and 2.5% negative lower than -1.96) and residual should not be correlated to the organ or global index.
- The variance associated with the random factor (between investigator variability) relatively to the residual variance (within investigator variability).

During the construction phase, apparently inconsistent data and data with high residuals were flagged, and investigators were asked to accurately review their damage evaluations.

For index validation, an internal cross-validation of the correlation between investigator damage evaluations and predicted damage indexes, calculated without taking account of the investigator random factor (as it will be used after the publication) was obtained as follows[11]: a bootstrap sample of size "n" was derived from the original sample of size "n" through resampling with replacement; the damage index was derived in the bootstrap sample and applied to the original sample; the correlation in the bootstrap sample minus the correlation computed in the original sample vwas an estimate of the optimism; the average optimism calculated from 1000 bootstrap samples was subtracted from the final model correlation to provide an expected bias-corrected correlation estimate.

In the inter-observer variation study, intraclass correlation coefficient (ICC) was used to assess the reproducibility level of the calculated organ indexes and Lémann Index using MRI data only (for more details, see Supplementary Materials, Methods section)[12,13]. The total variance of each index is also provided because ICC level is known to depend on total variance (ICC values can be compared, only when total variances are comparable).

The influence of disease duration on the Lémann Index distribution was tested globally through the Kruskal-Wallis method. The influence of clinical activity (CDAI relatively to 150) on the Lémann Index distribution per disease duration was tested through Mann-Whitney method. In addition, an interaction test was performed through 2-way analysis of variance to detect if the influence of clinical activity on the Lémann Index could vary according to disease duration.

The statistical analyses were carried out on 19.1 SPSS statistical software (SPSS, Chicago, IL).

RESULTS

Patients and Investigators

From August 2008 to December 2010, 381 patients were enrolled in 20 centers and 24 sets (4 centers were allowed to recruit a new set of 10 patients after having recruited a first set). As shown on the patient flow chart *(Supplementary Figure 1)*, 83 patients were excluded due to at least one major protocol deviation: lack of at least one mandatory investigation according to CD location at enrollment (n = 73) or time interval between the first and the last investigational methods >120 days (n = 10). Taking into account stratification of inclusion by disease location and duration, 175 patients were allocated in the construction phase. Only patients allocated in a set with at least 8 patients were retained in the construction phase. Finally, 138 patients enrolled in 12 centers corresponding to 14 sets (2 centers recruited 2 sets respecting the stratification of inclusion according to disease location and duration) were retained in the construction phase. A total of 100 patients (with same characteristics in terms of disease and duration than patients already allocated in the construction phase) were allocated in the forthcoming validation phase and 23 patients were not retained because they were not allocable (ie, same characteristics in terms of disease location and duration as patients already allocated in the construction or validation phase).

Table 2 : Baseline Characteristics of the 138 Patients Included in the Statistical Analysis.

Characteristics	
Females, n (%)	64 (46)
Age (y), median (IQR)	34 (26-45)
Time since diagnosis (y), median (IQR)	6 (1-14)
CDAI, median (IQR)	187 (102-267)
CDAI < 150, n (%)	50(36)
Known or suspected CD location, n (%)	
Upper digestive tract	20 (14)
Small bowel	102 (74)
Colon and/or rectum	83 (60)
Perianal	51 (37)
Duration of the disease, n (%)	
<2 years	45 (33)
≥2 and <10 years	46 (33)
≥10 years	47 (34)

The main baseline characteristics of the 138 included patients are described in *Table 2*.

All 138 patients had an abdominal MRI ; 32 patients had an upper endoscopy, 100 patients had a colonoscopy, 43 patients had a pelvic MRI, and 59 patients had a CT scan. Description of the distributions of damage components, including number of resected segments and number of segments with stricturing and penetrating lesions according to most severe grade, is summarized in *Table 3*. Two (2%), 45 (33%), and 40 (29%) patients had a history of duodenum, small bowel, and colon/rectum surgical resection, respectively; 1 (1%) patient had a proctectomy.

Constructing the Organ Indexes and the Lémann Index

In each of the 12 centers that enrolled the 138 patients retained for the construction phase, one gastroenterologist and one radiologist were asked to perform organ and global digestive tract damage evaluations.

Organ damage evaluations were calculated as the sum of the segmental damage evaluations (resections excluded) for patients with known or suspected organ damage at enrollment or with observed lesions during subsequent investigations: 24 for upper digestive tract, 115 for small bowel, 92 for colon/rectum, and 59 patients for anus. Mean (SD, range) organ damage evaluations were 2.7 (2.4, 0–7) for upper digestive tract, 6.8 (9.2, 0–77) for small bowel, 6.7 (6.4, 0–28) for colon/rectum, and 3.5 (1.9, 0–7.5) for anus.

Table 4 provides the coefficient estimates with their standard error and P value for each of the 4 organs, and the rounded coefficients that were applied to the number of segments with stricturing and penetrating lesions of each severity grade in order to calculate the pre-

Table 3: Distributions of Damage Components Including Number of Resected Segments or Number of Segments With Stricturing or Penetrating Lesions of Most Severe Grade (N = 138)

Organ	No. of Segments	Resection		Without stricturing and penetrating lesions	Stricturing lesions with maximal grade				Penetrating lesions with maximal grade			
		No	Yes		0	1	2	3	0	1	2	3
Upper tract	1	136	2*	117	130	0	4	4	118	11	3	2
	2		0			0	0	0		3	0	0
	3		0			0	0	0		1	0	0
Small bowel	1	93	18	40	44	12	40	23	102	NA	14	11
	2		14			3	7	6		NA	7	2
	3		9			2	4	4		NA	3	1
	>3		4			0	1	3		NA	1	0
Colon/rectum	1	98	22**	56	91	9	18	7	69	22	7	13
	2		8**			5	4	1		8	6	2
	3		1*			1	4	0		7	5	0
	>3		9***			1	9	0		5	11	0
Anus	1	137	1	82	121	6	9	2	87	22	22	7

*NA: not applicable, * Partial resection, ** Including 2 partial resections, *** Including 3 partial resections.*

Table 4 : Estimated and Final Coefficients to be Applied to the Numbers of Segments With Stricturing and Penetrating Lesions of Each Grade of Severity in Order to Calculate the Organ Indexes and to the Calculated Organ Damage Evaluations In Order to Calculate the Lémann Index

Organ	Type of lesion	Grade of severity	Coefficient		P value	Final coefficients*
			Estimate	SE		
Organ indexes						
Upper tract (n = 24)	Stricturing**	2	3.45	0.73	<.001	3.5
		3	3.70	0.98	<.001	3.5
	Penetrating	3	2.00	1.31	.14	2.0
Small bowel (n = 115)	Stricturing**	1	0.75	0.29	.012	1.0
		2	2.64	0.23	<.001	2.5
		3	4.48	0.14	<.001	5.0
	Penetrating	2	1.65	0.24	<.001	1.5
		3	4.01	0.36	<.001	4.0
Colon/rectum (n = 92)	Stricturing**	2	1.77	0.24	<.001	2.0
		3	5.54	0.77	<.001	5.5
	Penetrating	1	1.03	0.20	<.001	1.0
		2	2.64	0.21	<.001	2.5
		3	4.28	0.59	<.001	4.5
Anus (n = 59)	Stricturing**	2	1.58	0.37	<.001	1.5
		3	3.33	0.76	<.001	3.5
	Penetrating	2	2.44	0.29	<.001	2.5
		3	3.60	0.45	<.001	3.5
Lémann Index			**Calculated investigator organ-damage evaluation**			
Upper digestive tract			0.209	0.077	.008	2.0
Small bowel			0.521	0.071	<.001	5.0
Colon/rectum			0.344	0.028	<.001	3.5
Anus			0.331	0.025	<.001	3.5

** Final coefficients for organ indexes were obtained by rounding estimated coefficients; final coefficients for Lémann Index were obtained by multiplying estimated coefficients by 10 then rounding the obtained number.*

*** Whatever the length of the stricture, the number of segments with structuring lesions of length >5 cm for each severity grade was never selected into the model.*

dicted organ index (resections excluded, see text to take into account resections). It should be noted that the length of stricturing lesions did not play any role in the damage prediction in any organ. The intervention "major surgery leading to substantial anal sphincter damage" was never encountered in our sample. Therefore, we decided to give to this situation a score of 7.0, corresponding to the combination within the anal segment of a stricturing and penetrating lesions of grade 3.

The percentage of the variance of the calculated organ index explained by the model was 70%, 97%, 88%, and 76% for the upper digestive tract, the small bowel, the colon/rectum, and the anus, respectively. *Figure 1A* shows the scatterplot of the predicted index vs the damage evaluation given by the investigator for each of the 4 organs. The scatterplot of the residual as a function of the predicted organ index is presented per organ in *Supplementary Figure 2*. The estimates of the random factor and of the residual variances were 0.749 and 2.716, 2.094 and 5.078, 0.351 and 0.907 for small bowel, colon/rectum and anus, respectively. Residual variance estimate was 1.724 for the upper tract.

The investigator global damage evaluation ranged from 0 to 7, with a mean (SD) of 1.85 (1.50). *Table 4* provides the coefficient estimates of the global index with SE and P value and the final coefficients to be applied to the calculated organ damage evaluations in order to estimate the Lémann Index. The percentage of the variance of the investigator global damage evaluation explained by the global index was 81%. *Figure 1* shows the scatterplot of the global index vs the investigator global damage evaluation. The scatterplot of the residual as a function of the predicted global index is presented in *Supplementary Figure 3*. The estimates of the variance of the random factor and of the residual variance were 0.299 and 0.364, respectively.

One example of the calculation of the 4 organ indexes and of the Lémann Index is given in *Table 5*. In practice, Lémann Index could be easily calculated using an Excel file (to make the calculation of the Lémann Index straightforward, an Excel worksheet is available on request).

Internal Validation of the Lémann Index

The overestimation of the correlation co efficient between predicted damage index and investigator damage evaluation, when estimated on the same sample as the one used to construct the index, was derived from the bootstrap method to 0.012, 0.002, 0.008, and 0.008, for the upper tract, small bowel, colon/rectum, and anus, respectively, and to 0.005 globally. The unbiased correlation coefficients between predicted indexes and investigator damage evaluations were 0.85, 0.98, 0.90, 0.82, for upper tract, small bowel, colon/rectum, anus, respectively, and 0.84 globally, as shown in *Figures 1A and B*.

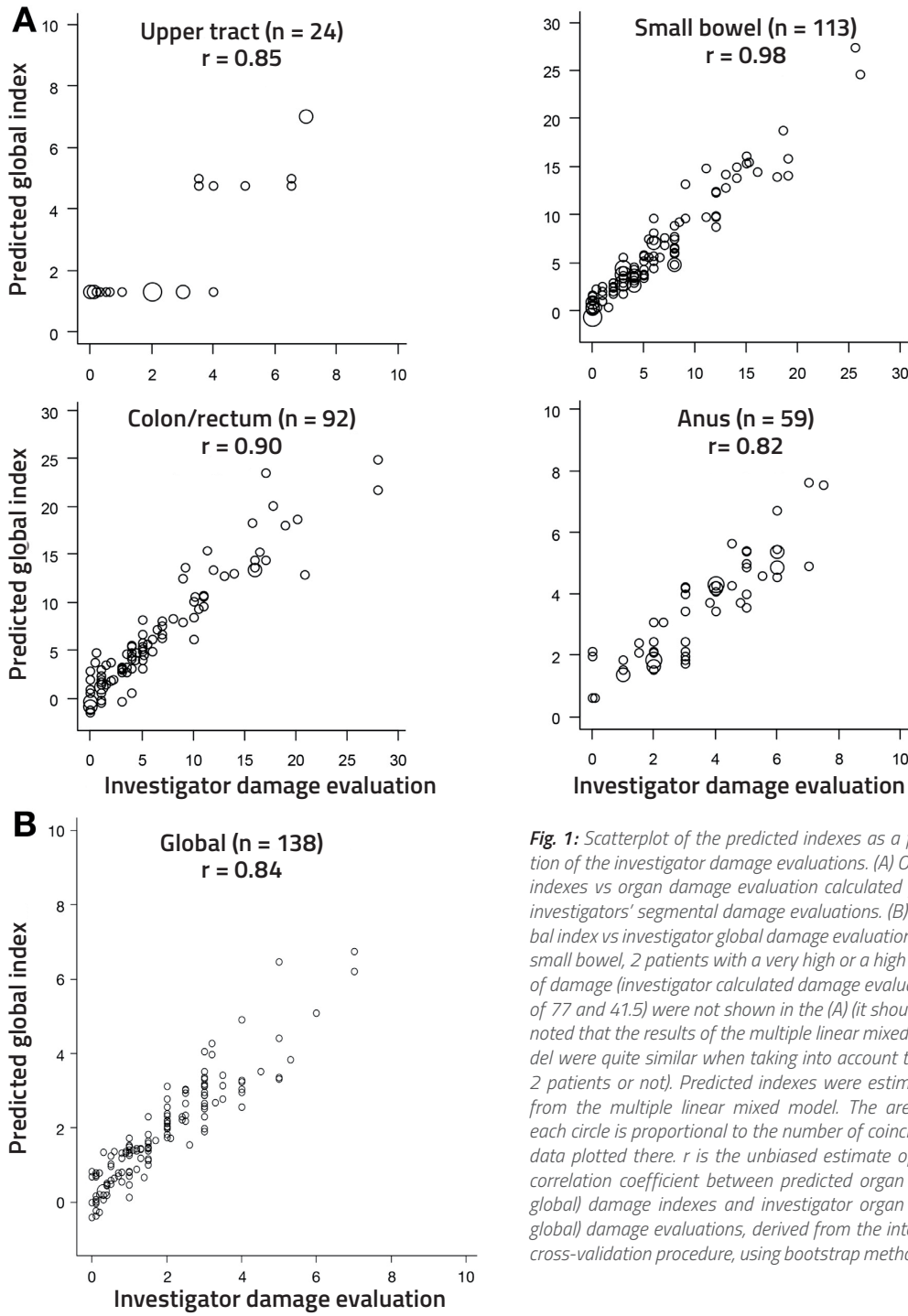

Fig. 1: *Scatterplot of the predicted indexes as a function of the investigator damage evaluations. (A) Organ indexes vs organ damage evaluation calculated from investigators' segmental damage evaluations. (B) Global index vs investigator global damage evaluation. For small bowel, 2 patients with a very high or a high level of damage (investigator calculated damage evaluation of 77 and 41.5) were not shown in the (A) (it should be noted that the results of the multiple linear mixed model were quite similar when taking into account these 2 patients or not). Predicted indexes were estimated from the multiple linear mixed model. The area of each circle is proportional to the number of coincident data plotted there. r is the unbiased estimate of the correlation coefficient between predicted organ (and global) damage indexes and investigator organ (and global) damage evaluations, derived from the internal cross-validation procedure, using bootstrap method.*

Table 5 : Example of Lémann Index Calculation
(Lémann Index Ranged Between 0, No Damage, and 140, Maximal Damage)

Segment and organ	Resection %	Stricturing lesions				Penetrating lesions				Index
		gr. 1	gr. 2	gr. 3	Index*	gr. 1	gr. 2	gr. 3	Index*	
Esophagus					0				0	0
Stomach					0				0	0
Duodenum					0				0	0
Upper tract (sum of segmental indexes / 3)										0.0**
Small bowel 1	X				0				0	10
Small bowel 2	X				0				0	10
Small bowel 3	X				0				0	10
Small bowel 4				X	5				0	5
Small bowel 5				X	5			X	4	9
Small bowel ...					0				0	0
Small bowel 20					0				0	0
Small bowel (sum of segmental indexes / 20)										2.2**
Cecum					0				0	0
Ascending colon					0				0	0
Transverse colon					0				0	0
Descending colon					0				0	0
Sigmoid colon					0				0	0
Rectum					0				0	0
Colon/rectum (sum of segmental indexes / 6)										0.0**
Anus				X	3.5				0	3.5
Anus (1 segment)										3.5**
Lémann Index										23.3***

NOTE: *Male patient aged 58 years, with frank anal stricture (grade 3), 58 cm of small bowel previous resected (3 segments of 20 cm), and 2 segments with stricture and prestenotic dilatation (grade 3), one with a fistula (grade 3), of the small bowel.*

** For index calculation per segment, please see rounded coefficients in Table 4.*

*** Calculated for each organ by dividing the sum of segmental indexes by the number of segments.*

**** The weight of each organ in the Lémann Index is obtained by multiplying each organ index by its final coefficient, as presented in Table 4.*

Inter-Observer Variation Study of the Organ Damage Indexes and of the Lémann Index

Six pairs of investigators (1 gastroenterologist and 2 radiologist within each of the 6 centers) participated in this study. ICC estimates were 0.25 (95% confidence interval [CI]: 0.09–0.42), 0.54 (95% CI : 0.39–0.67), 0.57 (95% CI : 0.43–0.70), and 0.72 (95% CI : 0.55–0.85) with a total variance of 0.48, 33.37, 27.12, and 2.25 for organ indexes, upper tract, small bowel, colon/rectum, and anus, respectively.

For the Lémann Index, ICC estimate was 0.60 (95% CI : 0.47–0.72) with a total variance of 22.99.

Lémann Index by Disease Duration and Clinical Activity

The median Lémann Index significantly increased with disease duration (global test, P < 0.001): 6.3 (IQR, 1.8–15.4), 14.3 (IQR, 5.9–20.0), and 19.0 (IQR, 8.8–29.0) for disease duration <2 years, ≥2 and <10 years, and ≥10 years), respectively *(Fig. 2)*.

Clinical disease activity at the enrollment using CDAI had no significant influence on the distribution of the Lémann Index, when taking into account disease duration, with median values among patients with CDAI ≤ 150 and among patients with CDAI >150 as follows: 5.7 and 6.3 for disease duration <2.0 years, 13.2 and 14.8 for disease duration between 2.0 and 10.0 years, and 19.3 and 17.5 for disease duration ≥10 years (P = .84, .25, and .93, respectively). Statistical analysis did not find that the impact of clinical disease activity on the distribution of the Lémann Index varied with disease duration (interaction test, P = .71).

DISCUSSION

The Lémann Index is the first tool that measures the cumulative bowel damage by using resections and the extent and severity of lesions in the digestive tract of CD patients. In contrast to other indexes that are based only on clinical or endoscopic data and assess the severity of inflammatory activity at a specific time and fluctuate with time, the Lémann Index is more likely to increase with the longer disease duration by assessing irreversible bowel damage along with accumulation of stricturing lesions, penetrating lesions, and surgical resections. In this study, we actually found that the median Lémann Index increases with disease duration.

We evaluate CD damage by taking into account resection and stricturing and penetrating lesions within segment, including segments with previous bypass diversion or stricturoplasty, assuming that only the status of the segment after surgical intervention is relevant in terms of damage.

To assess CD damage, appropriate imaging modalities should be used such as endoscopy and cross-sectional imaging. Still, the number of imaging techniques should be limited to facilitate widespread use of the index, and ideally a single technique should be selected. MRI and CT have been reported to have similar accuracy in diagnosing CD of the small bowel but MRI offers the benefit of high accuracy, lack of ionizing radiation, and ability to be repeated in time[14]. Although colonoscopy was required in our study in patients with a history of colonic involvement, encouraging results have been reported regarding the ability of MRI to assess colonic disease in CD[15]. If confirmed, the Lémann Index could be based on MRI alone in the future.

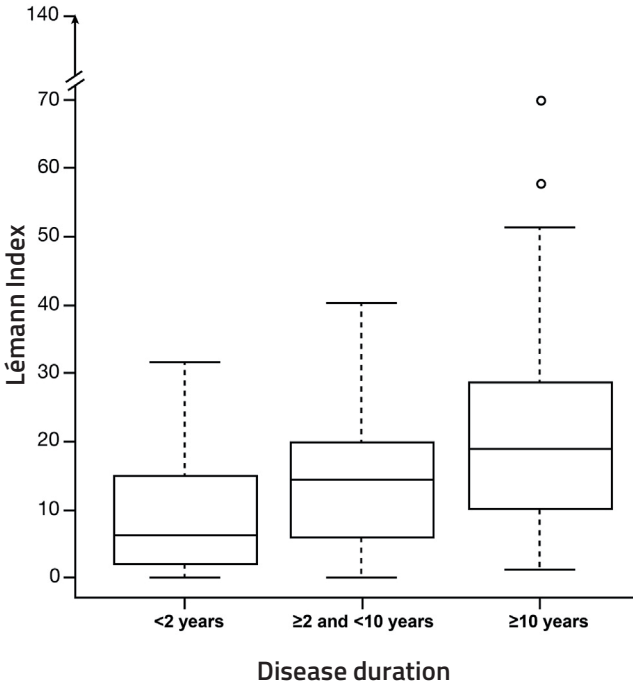

Fig. 2: *Boxplot of Lémann Index according to disease duration. Box reflects the median, first, and third quartiles, and whiskers the 95% CI. Lémann Index was calculated using the final coefficients (see Table 4).*

The evaluation of cumulative digestive damage in CD is a new concept for gastroenterologists. This likely explains the methodological difficulties we initially encountered when developing the Lémann Index. Two strategies were successively tested to evaluate damage at an organ level. Clinicians were first asked to evaluate the damage at an organ level taking into account both the severity and the extent of the damage in all segments of the whole organ as evaluated by different imaging techniques and clinical assessment (anus). This led to numerous inconsistencies in the organ damage evaluation, most likely explained by the complexity of the data to be integrated. In order to facilitate a standardized calculation of organ damage, each investigator was also asked to evaluate damage at a segment level with a scale ranging from 0 to 10, and the organ damage was subsequently calculated as the sum of the segmental damage evaluations.

Multiple linear mixed modeling was used to derive the organ and global indexes, because assessment of different patients by the same investigator could not be considered as independent. In addition, the use of a random-effect factor to describe investigators (each fac-

tor value being a realization of this random variable drawn from a Gaussian centered distribution) allows this index to be applied universally by any group of investigators or clinicians, if drawn from the same population, as opposed to an index that uses a fixed-effect factor.

The different organ indexes derived from the linear mixed model showed a good fit with the investigator organ damage evaluations *(Fig. 1A)*. The scatterplot of residuals as a function of predicted organ indexes did not show any trend of deviation from the necessary following assumptions (distribution with constant variance, not correlated with predicted values). The variance associated with random-effect factor was between 25% and 40% of the residual variance, showing a rather large variation across investigators, but still reasonable relative to residual variation. The global Lémann Index derived from the linear mixed model showed a good fit with the investigator global damage evaluation *(Fig. 1B)*. The variance associated with random-effect factor was almost as high as residual variance (0.30 vs 0.36), showing a very large variation across investigators, at the same level as intra-investigator residual variation. These results stress the importance of creating a standardized global index due to the very large inter-investigator variation in this study.

In order to get unbiased estimates of the qualities of the damage indexes, we performed an internal crossvalidation subanalysis by using the bootstrap methodology, providing very satisfactory results. As our index measures cumulative bowel damage in the CD patient over a period of time, and not just the clinical condition of patient at some point of time, we did not have any indicator to establish external validity.

Because reproducibility is an important quality for a new index, in parallel with validity and sensitivity to change, we undertook an inter-observer variation study of organ and global indexes according to stricturing and penetrating lesions per grade at MRI examination only, because only MRI examinations were video-recorded. This approach was preferred to an inter-observer variation study of each stricturing and penetrating of each grade. Indeed, a given lesion of a given grade detected within a segment by one pair and not by another results in a change in the segmental index and then on the organ and global indexes. In addition, if a grade 3 lesion observed by one pair is missed by another pair, it is more likely that the later observed a grade 2 lesion than no lesion at all, resulting in a much smaller difference in segmental, organ, and global indexes.

There are several limitations to our study. First, we arbitrarily divided digestive tract into 4 organs and each organ into segments. For upper digestive tract, colon/rectum, and anus, this segmentation respects the anatomic segmentation of these organs. For the small bowel, we consensually choose 20 segments of 20 cm, because resection <20 cm is uncommon. Second, due to the small sample size of the upper tract subsample (n = 24), we were not able to estimate the investigator variance and reproducibility level estimate of the upper tract index is doubtful. In addition, the rarity of penetrating lesions of maximal grade led us

to introduce in the index grade 3 penetrating lesions, although not significant in the model. This should be confirmed in forthcoming studies. Third, in spite of the internal cross-validation performed, the Lémann Index needs to be further validated (the validation cohort is in progress), in an independent new sample, ideally with new investigators. Fourth, reproducibility levels of the organ and Lémann Indexes appeared to be lower than that of most already published indexes[16,17]. It should be acted that damage evaluation is something new in CD, as attested by the difficulties encountered in data recording that led to change our strategy to evaluate organ damage. It requires the skill of interpreting several examinations and integrating results from these various examinations, not a straightforward procedure. Our study involved gastroenterologists and radiologists from various centers in different countries, leading to larger interobserver variation in lesion detection than studies performed in a unique center, in which multiple readers are likely to have more similar behaviors. Consequently, it is likely that the organ and Lémann Indexes are not applicable everywhere, because it relies entirely on a standardized procedure for data recording, which must be learned beforehand. This difficulty, recognized by all authors, who had developed indexes even when using a unique examination, is in fact the reflection of the complexity of CD pictures at examinations, and as such each seems difficult to circumvent.

In conclusion, the first CD digestive tract damage index, the Lémann Index, is now available. Provided further validation and demonstration of sensitivity to change, the Lémann Index will allow us to measure the long-term impact of CD, to examine patients' heterogeneity in term of disease progression, to identify parameters associated at diagnosis with a high risk of rapid progression, and to measure the impact of different therapeutic strategies on the long-term outcome of CD patients.

SUPPLEMENTARY MATERIAL

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at http://dx.doi.org/10.1053/ j.gastro.2014.09.015.

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REPRINT REQUESTS

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CONFLICT OF INTERESTS

These authors disclose the following: Benjamin Pariente has received speaker fees from AbbVie and MSD. Jean-Yves Mary has received lecture and consultation fees from AbbVie and Janssen and consultation fees from Pharmacosmos. Silvio Danese is a speaker, consultant, and advisory board member for Schering-Plough, Abbott Laboratories, Merck & Co, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alphawasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Phar-

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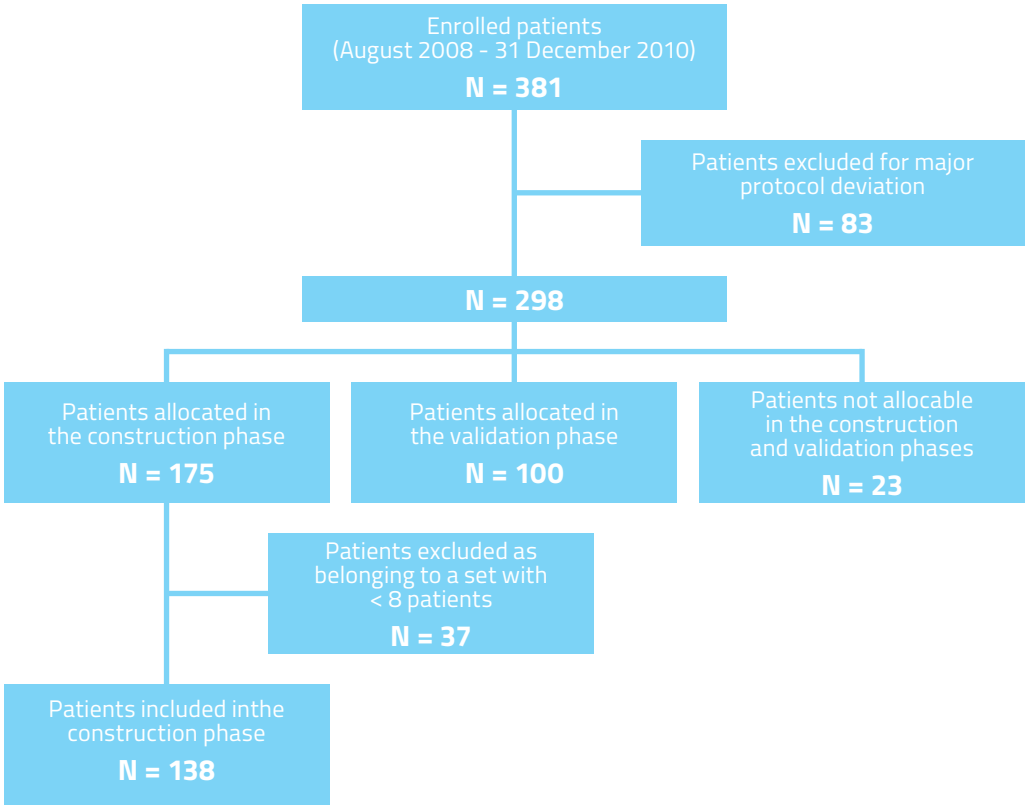
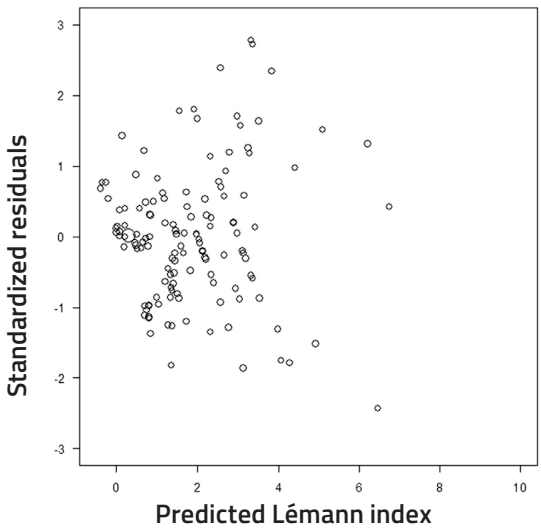
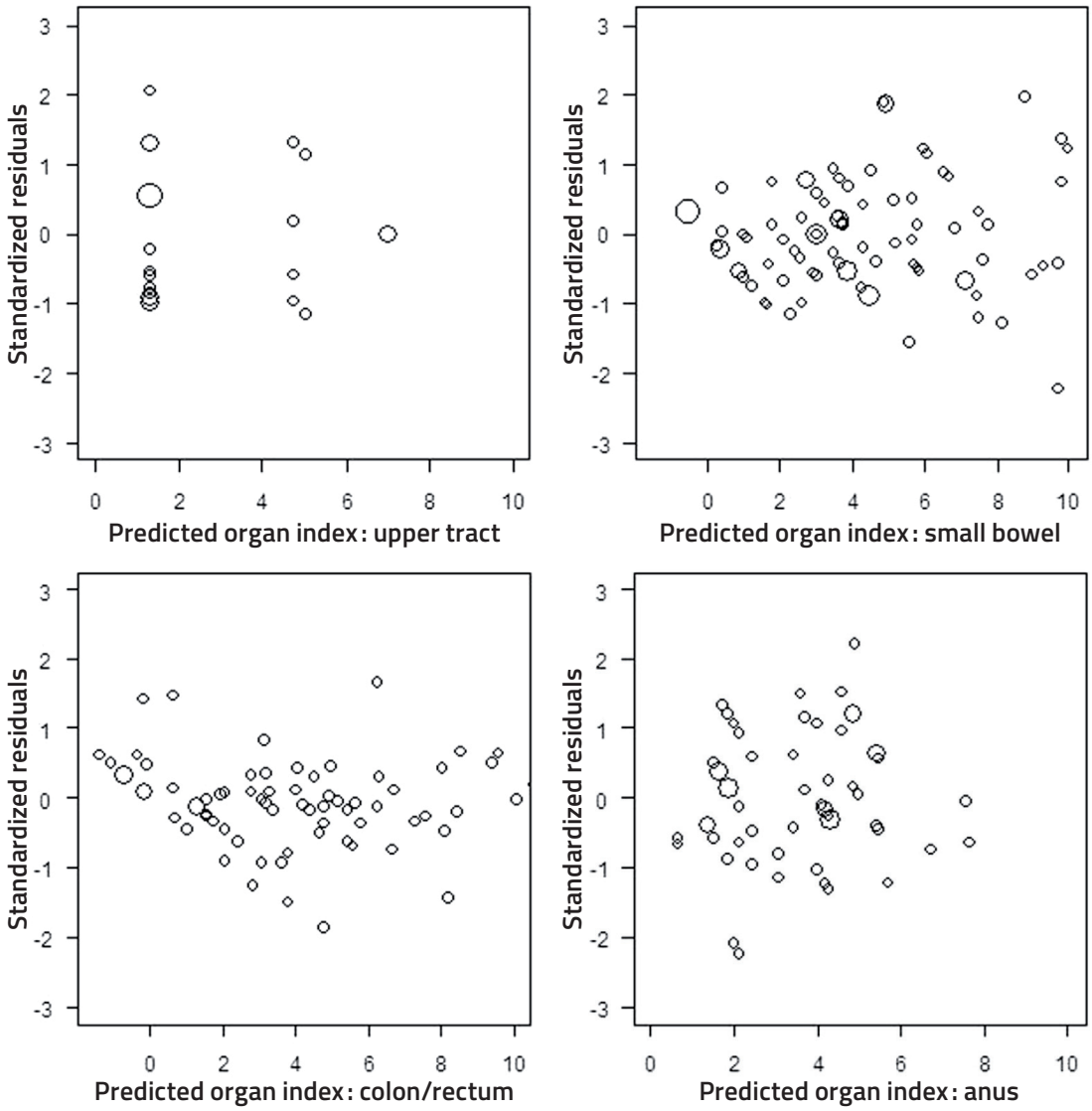


Supplementary Figure 1: Subject disposition



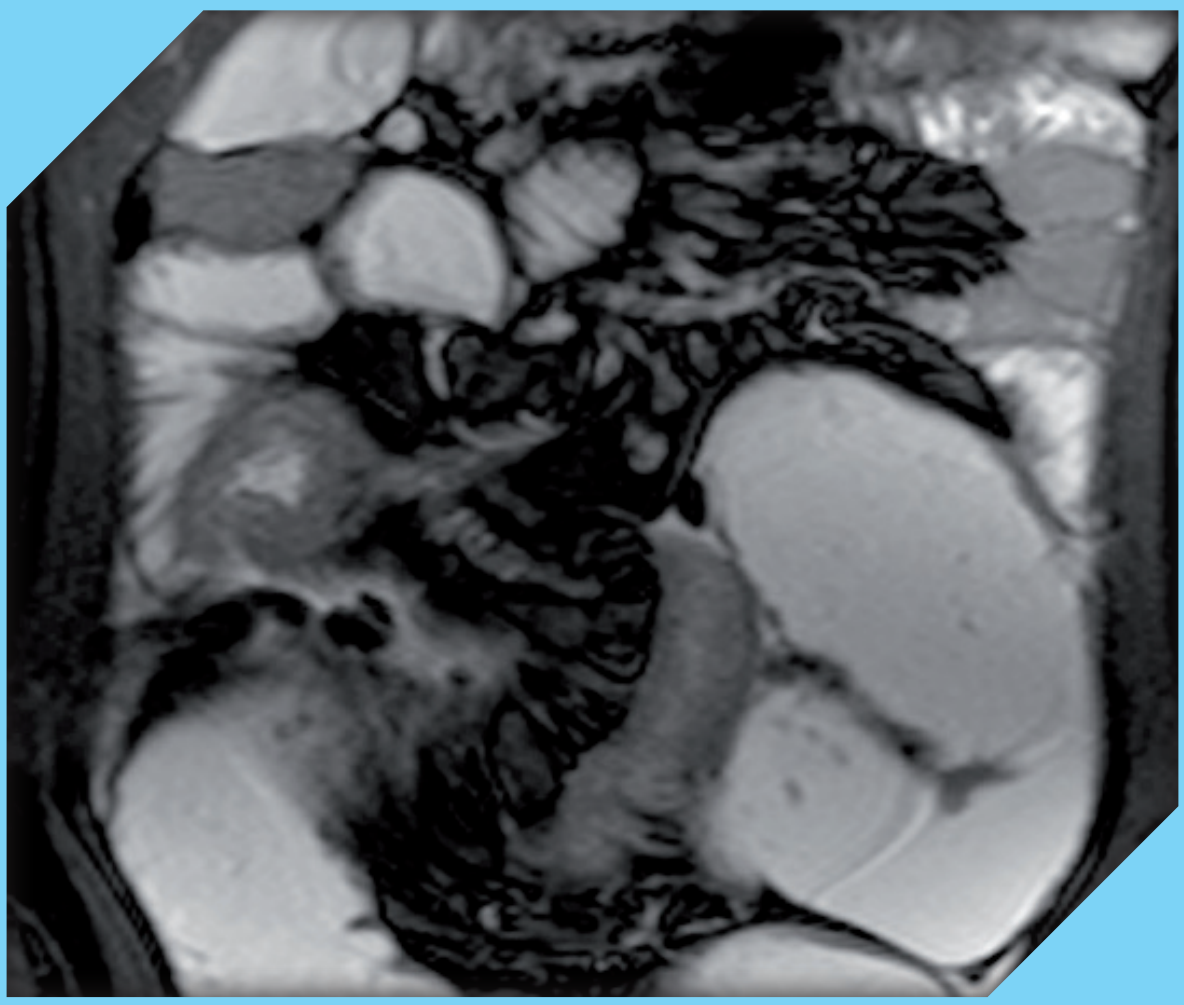
Supplementary Figure 3: *Scatterplot of the standardized residuals as a function of the predicted global index. The area of each circle is proportional to the number of coincident data plotted there.*



Supplementary Figure 2: *Scatterplot of the standardized residuals as a function of the predicted organ indexes. The area of each circle is proportional to the number of coincident data plotted there.*

Article 3

Depth of remission in Crohn's disease patients seen in a referral centre : associated factors and impact on disease outcome



Depth of remission in Crohn's disease patients seen in a referral centre : associated factors and impact on disease outcome

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Abstract

Introduction : **Our goals were to assess the prevalence of biological and tissue remission in routine practice in Crohn's disease, and to evaluate the correlation between biological or tissue remission and clinical or demographic characteristics as well as their impact on disease outcome.**

Methods : **We performed a retrospective monocenter study. Biological remission was defined by a CRP < 5 mg/l. Tissue remission was defined by the absence of ulcer at endoscopy and/or absence of signs of acute inflammation at MRI. Association with demographic, clinical and laboratory markers was studied by logistic regression models and rates of relapses, hospitalizations and surgeries were compared using the logrank test.**

Results : **Among the 263 patients included, 147 were in clinical remission ; 102/147 (69%) were in biological remission. Fifty-six patients also had morphological evaluation : 37 (66%) were in tissue remission. Biological remission was associated with older age, higher hemoglobin and lower BMI. Tissue remission was associated with older age, lower platelets count, absence of previous surgery, and the use of immunosuppressant. Time-to-relapse was significantly longer in patients with biological remission and in patients with tissue remission as compared to patients without biological or tissue remission.**

Conclusions : **Among the patients in clinical remission seen as outpatients, two thirds were either in biological and/or tissue remission. Biological and/or tissue remission was associated with a better outcome than clinical remission alone.** (Acta gastroenterol. belg., **2014**, 77, **41-46**).

Key words : Crohn's disease, endoscopy, magnetic resonance imaging, CT Scanner, C-reactive protein, deep remission.

Introduction

Crohn's disease (CD) is an inflammatory bowel disease characterized by alternative periods of remission and relapse. Remission can be judged at the clinical, biological or at the intestinal tissue level. There is no good correlation between clinical remission, biological remission and intestinal healing in CD (1). Indeed, during periods of clinical remission, endoscopic/imaging abnormalities can persist. Biomarkers such as C-reactive protein (CRP) or fecal calprotectin are better but still imperfectly correlated to tissue healing (2). Preliminary data indicate that persisting intestinal lesions despite clinical remission may lead to a higher risk of disease relapse and disease progression with worsening of tissue damage (3,4,5). The evolving concept of deep remission may include clinical but also biological remission and intestinal healing. This state could be associated with better disease outcome, with lower risk of relapse, hospitalizations and surgeries. Data from the EXTEND study indicate that with current treatment strategies, usually using anti-TNF late in the disease course, a deep remission combining clinical remission and mucosal healing can only be achieved in a minority of patients (6). This deep remission seems more frequently achieved when anti-TNF are used earlier in the disease (7). Currently, it is not precisely known what is the proportion of patients achieving such state of deep remission in routine practice, what are the factors associated with it and its influence on mid- and long-term disease outcome.

In this retrospective study we aimed at assessing the prevalence of biological and/or tissue remission in CD, in routine practice in a referral centre. Secondary objectives were to evaluate the correlation between biological and/or tissue remission and disease outcome, including relapses, hospitalizations and surgeries, and to try to find biological, clinical or demographic factors associated with it.

Patients and methods

We performed a retrospective study at the referral IBD center of Liège University Hospital in Belgium, and including patients seen at the outpatient clinic between April 2009 and April 2010. All consecutive patients seen during that period of time by two senior gastroenterologists (JB and EL) were first considered. Retrospective follow-up was then analyzed till October 2011. Protocol was accepted by University of Liège ethics committee. Among the patients seen at the outpatient IBD clinic of our hospital, we've selected a population of CD patients in clinical remission and having had a measurement of blood CRP. Some of those had also a tissue healing assessment by ileo-colonoscopy and/or intestinal MRI and/or CT-scanner within a short interval of time. Different stages of remission were compared : clinical only *vs* biological and clinical vs. tissue and clinical. Clinical remission was defined by a Harvey Bradshaw Index

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(HBI) ≤ 4 or absence of CD symptoms according to clinician judgment in the medical notes of the patient. All the patients included in our analyses were considered in clinical remission. Biological remission was defined by a CRP < 5 mg/l. Tissue remission was defined by the absence of ulcer at endoscopy and/or absence of signs of acute inflammation at magnetic resonance imaging (MRI) or CT scanner (mucosal or submucosal edema, early contrast enhancement, mucosal ulcers, fat stranding, comb sign). A relapse was defined, either by the need to change therapy due to symptoms worsening, hospitalization due to CD, endoscopic dilatation of a gastrointestinal tract stricture, or surgical procedure for the disease (including bowel resection, stoma and perianal abscess drainage). The outcome was assessed using the time-to-relapse or the time to more specific outcomes, such as hospitalization or surgery.

Logistic regression models were used to measure the association between the different predefined states of remission with demographic, clinical and laboratory markers. Rates of relapses over follow-up were represented on Kaplan-Meier curves and compared with logrank test. Multivariate Cox regression models were used to explain rates of relapses with covariates. P values were considered as significant at the 5% level ($p < 0.05$). Calculations were done using SAS version 9.2 (SAS Institute, Cary, NC, USA).

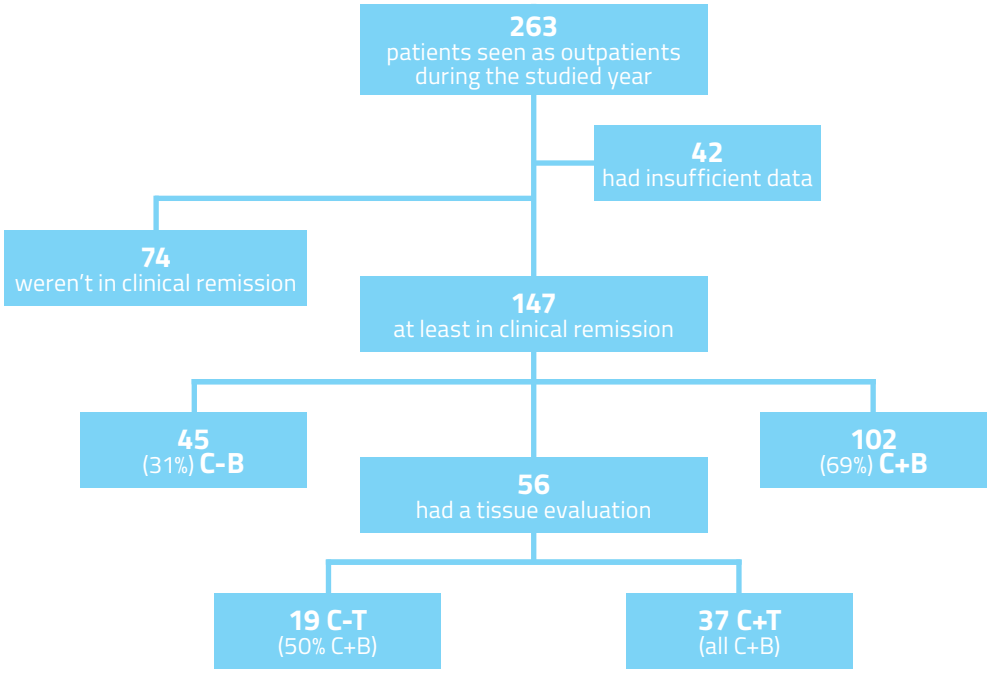

Fig. 1: *CD patients' disposition in the study. Among the 147 studied patients, 56 had endoscopic and/or MRI exploration. Among those, 37 showed mucosal (at endoscopy) and/or bowel wall (at MRI) healing and were considered in tissue remission. All of these also happened to be in biological remission.*

Table 1 : Patients characteristics of the studied population (C-B and C+B; n = 147) and the subpopulation with endoscopic and/or MRI-CT assessment (C+T and C-T; n = 56). Data expressed as n (%) or mean ± SD

		C-B (n = 45)	C+B (n = 102)		C+T (n = 37)	C-T (n = 19)	
Gender	F	34 (75.6)	49 (48.0)		19 (51.4)	9 (47.4)	
	M	11 (24.4)	53 (52.0)	**	18 (48.7)	10 (52.6)	
Age	yrs	37.1 ± 12.3	42.2 ± 13.3	*	43.4 ± 13.2	35.8 ± 13.8	
Disease duration	yrs	11.2 ± 6.76	13.3 ± 9.27		12.8 ± 9.59	9.95 ± 6.84	
BMI		25.1 ± 4.95	23.8 ± 3.68		24.3 ± 4.41	24.7 ± 4.85	
Smoking	No	21 (46.7)	34 (33.7)		16 (43.2)	7 (36.8)	
	Yes	19 (42.2)	38 (37.6)		11 (29.7)	9 (47.4)	
	ex	5 (11.1)	29 (28.7)	*	10 (27.0)	3 (15.8)	
Montreal classification							
A	1	4 (8.9)	8 (7.8)		3 (8.1)	0 (0.0)	
	2	36 (80.0)	78 (76.5)		27 (73.0)	18 (94.7)	
	3	5 (11.1)	16 (15.7)		7 (18.9)	1 (5.3)	
B	1	27 (60.0)	57 (56.4)		22 (59.5)	8 (42.1)	
	2	7 (15.6)	25 (24.8)		9 (24.3)	6 (31.6)	
	3	11 (24.4)	19 (18.8)		6 (16.2)	5 (26.3)	
L	1	10 (22.2)	33 (32.7)		14 (37.8)	5 (26.3)	
	2	10 (22.2)	19 (18.8)		5 (13.5)	2 (10.5)	
	3	20 (44.4)	43 (42.6)		15 (40.5)	7 (36.8)	
	4	1 (2.2)	2 (2.0)		1 (2.7)	1 (5.3)	
	1+4	3 (6.7)	3 (3.0)		1 (2.7)	3 (15.8)	
	3+4	1 (2.2)	1 (1.0)		1 (2.7)	1 (5.3)	
P	No	25 (55.6)	68 (66.7)		24 (64.9)	10 (52.6)	
	Yes	20 (44.4)	34 (33.3)		13 (35.1)	9 (47.4)	
Laboratory parametrers							
Platelets	10^9/L	335 ± 92.2	291 ± 94.9	*	289 ± 67.0	327 ± 68.0	*
Hemoglobin	g/dL	12.9 ± 1.09	13.9 ± 1.30	**	14.0 ± 1.06	13.1 ± 1.26	**
CRP	mg/L	12.9 ± 10.4	1.64 ± 1.28	***	1.42 ± 1.17	7.18 ± 10.1	***

	C-B (n = 45)	C+B (n = 102)	C+T (n = 37)	C-T (n = 19)	
Treatment					
Previous surgery	25 (55.6)	55 (53.9)	18 (48.6)	13 (68.4)	
Anti-TNF	25 (55.6)	46 (45.1)	13 (35.1)	11 (57.9)	
Mesalazine	4 (8.9)	18 (17.6)	7 (18.9)	4 (21.0)	
Topical steroids	4 (8.9)	7 (6.9)	2 (5.4)	2 (10.5)	
Immunosuppressant	14 (31.1)	34 (33.3)	14 (37.8)	1 (5.3)	*
Systemic steroids	4 (8.9)	4 (3.9)	1 (2.7)	2 (10.5)	
No treatment	1 (2.2)	8 (7.8)	4 (10.8)	1 (5.3)	

**p < 0.05 ; **p < 0.01 ; ***p < 0.001.*

C-B: clinical remission without biological remission ; C+B = clinical and biological remission ; C-T = clinical without tissue remission; C+T:clinical and tissue remission.

RESULTS

Among the 263 CD identified in outpatients track records for the considered year, 147 were at least in clinical remission (C) and had a measurement of blood CRP. The characteristics of these 147 patients are showed in *Table 1*. Among them, 102 (69%) were in clinical and biological remission (C+B). Out of 147, only 56 patients had undergone a morphological exploration. As such kind of morphological exploration is not yet systematic in routine practice, it was only performed in a subset of patients after an agreement between the patient and physician to assess tissue healing. There was no other specific indication for this exploration and this subpopulation was not different form the global population. Among these 56 patients having had morphological evaluation (either by endoscopy (n = 35), MRI or CT (n = 21)), 37 were in clinical and tissue remission. All the patients in tissue remission were also in biological remission (C+B+T) *(Fig. 1)*. Among the 19 patients not being in tissue remission, 10 were in biological remission.

Factors associated with biological remission (n = 147)

By univariate analysis, male gender (OR = 3.34, 95% CI = 1.53-7.32 ; p = 0.0025), older age (OR = 1.04, 95% CI = 1.01-1.07 ; p = 0.011), being a former smoker (OR = 3.58, 95% CI = 1.20-10.70 ; p = 0.022), lower platelet counts (OR = 0.13, 95% CI = 0.03-0.54 ; p = 0.049), and higher hemoglobin (OR = 2.07, 95% CI = 1.47-2.92 ; p < 0.0001) were associated with biological

remission. In multivariate analysis (performed on 140/147 patients), older age (OR = 1.04, 95% CI = 1.00-1.08 ; p = 0.02), higher hemoglobin (OR = 2.16, 95% CI = 1.50-3.10 ; p < 0.0001) and lower Body Mass Index (BMI) (OR = 0.88, 95% CI = 0.81-0.98 ; p = 0.01) were associated with biological remission.

Factors associated with tissue remission (n = 56)

By univariate analysis, the absence of ANCA (OR = 0.10, 95% CI = 0.01-0.74 ; p = 0.025), a lower platelets count (OR = 0.06, 95% CI = 0.00-0.91 ; p = 0.043), a higher hemoglobin (OR = 1.97, 95% CI = 1.11-3.50 ; p = 0.020), a lower CRP (OR = 0.28, 95% CI = 0.13-0.57 ; p = 0.0006) and the use of immunosuppressive drugs (OR = 11.0, 95% CI = 1.32-91.31 ; p = 0.027) were associated with tissue remission. In multivariate analysis (performed on 54/56 patients), older age (OR = 1.08, 95% CI = 1.00-1.17 ; p = 0.03), lower platelets count (OR < 0.001, 95% CI = < 0.00-0.16 ; p = 0.008), absence of previous surgery (OR = 0.12, 95% CI = 0.02-0.85 ; p = 0.03), and the use of immunosuppressant (OR = 145.54, 95% CI = 3.42- > 999.99 ; p = 0.009) were associated with tissue remission.

Time-to-relapse according to the state of Crohn's disease remission

Time-to-relapse was significantly longer in patients with biological remission (C+B) as compared to patients without biological remission (C-B) (median time to relapse > 30 months vs. 20 months ; p = 0.0008) *(Fig. 2)*. Beside the absence of biological remission, using bivariate model, the significant variables associated with a shorter time to relapse were the B2 phenotype at last visit (HR = 2.04, 95%CI : 1.14-3.65, p = 0.016), a lower hemoglobin (HR = 1.30, 95%CI : 1.04-1.63, p = 0.022), current anti-TNF treatment (HR = 1.90, 95%CI : 1.11- 3.23, p = 0.018), and current systemic corticoid treatment (HR = 2.38, 95%CI : 1.11-3.23, p = 0.049).

When considering only the subset of patients with morphological assessment of tissue healing (n = 56), time-to-relapse was significantly longer in patients with tissue remission (being in this study population systematically associated with biological remission (C+B+T)), as compared to patients without tissue remission (C-T) (median time to relapse > 29 months vs. 22 months ; p = 0.0043) *(Fig. 3)*.

Beside tissue remission, using bivariate model, no other variable was significantly associated with the time-to-relapse. In the small subgroup of patients in biological but not tissue remission (n = 10/56) the relapse rate over follow-up was 50% (5/10) as compared to 21.7% (8/37) in patients in both biological and tissue remission.

Time-to-surgery and time-to-hospitalization according to the state of remission

Biological remission tended to be associated to a low (p = 0.06) but not with a lower risk of hospitalization *(Fig. 4)*.

Tissue remission (here systematically associated with biological remission) was associated to a lower risk of surgery (p = 0.04) but not of hospitalization *(Fig. 5)*.

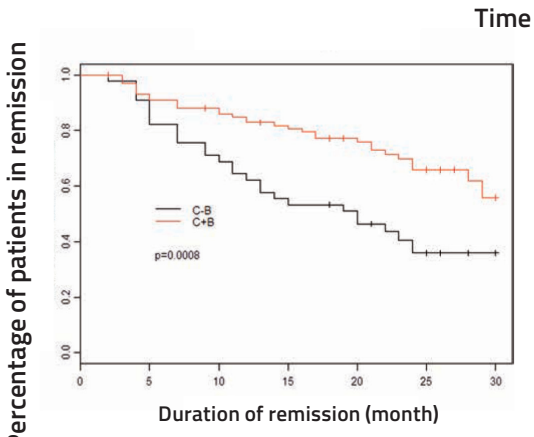

Fig. 2: *Kaplan Meier curves of time to relapse for the patients with clinical and biological remission (C+B ; n = 102) vs. patients with clinical but not biological remission (C-B ; n = 45).*

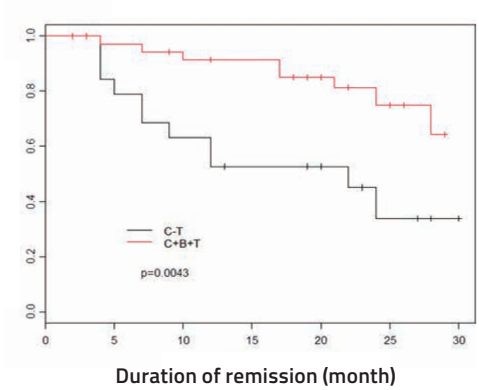

Fig. 3: *Kaplan Meier curves of the time to relapse in patients with clinical and tissue remission (C+T ; n = 37) vs. patients with clinical but not tissue remission (C-T ; n = 19). The 37 patients with clinical and tissue remission (C+T) happened to be also in biological remission (C+B+T).*

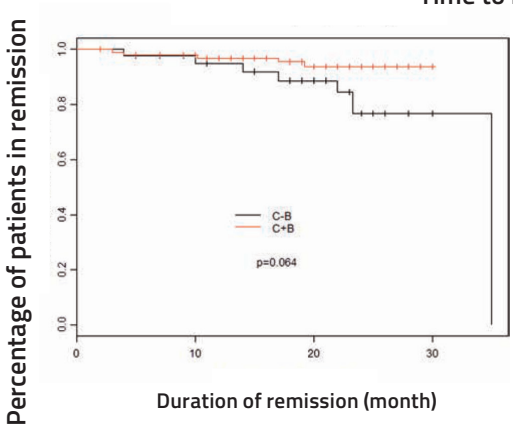

Fig. 4: *Kaplan Meier curves of the time to surgical resection in patients with clinical and biological remission (C+B ; n = 102) vs. patients with clinical but not biological remission (C-B ; n = 45).*

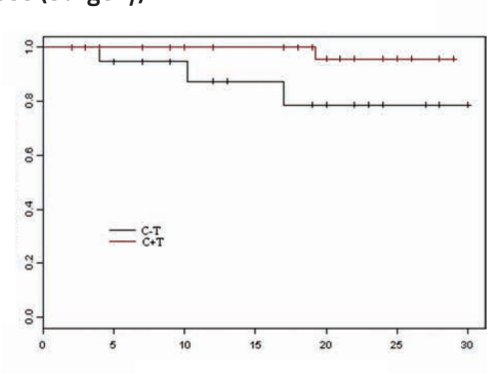

Fig. 5: *Kaplan Meier curves of the time to surgical resection in patients with clinical and tissue remission (C+T ; n = 37) vs. patients with clinical but not tissue remission (C-T ; n = 19). The 37 patients with clinical and tissue remission (C+T) happened to be also in biological remission (C+B+T).*

DISCUSSION

Among the patients seen as outpatients, in clinical remission, in our center in 2009, we found a proportion of two thirds who were in biological and/or tissue remission. This state of remission beyond clinical symptoms was associated with better outcome including less relapses and less surgeries.

The prevalence of deep remission defined by the occurrence of both clinical and biological remission and/or intestinal tissue healing has not been broadly studied in routine practice in CD. In a prospectively recruited cohort of CD patients in clinical remission under combination therapy with infliximab and immunosuppressants, more than ¾ were also in biological remission (defined by a hsCRP < 5 mg/l) and more than ⅔ were in mucosal healing (defined either by the absence of ulcer or a CDEIS < 3)[5]. This is very close to what we observed, in a relatively similar population since around 80% of our patients were treated with anti-TNF and/or immunosuppressants. The proportion of deep remission may be much lower in patients treated with corticosteroids[1], in more severe patients, or patients not responding optimally to anti-TNF and/or immunosuppressants. In a population-based study from Norway, including CD cases diagnosed in the early nineties, before the era of anti-TNF, only 38% were in mucosal healing one year after the diagnosis[4]. Steroid treatment was associated with a lower rate of mucosal healing. In a recently published controlled trials comparing adalimumab to placebo for the induction and maintenance of mucosal healing in CD, only around 20% of the patients achieved such level of remission including clinical remission and mucosal healing[6].

Biological remission is known to be associated with an older age[8]. Low platelet count and a higher hemoglobin concentration have already been associated with good outcome in CD including a low risk of developing severe disease and lower risk of relapse[5,9,10]. In a post-hoc analysis of the EXTEND trial, it was also associated with mucosal healing[7]. A more surprising association may be the one between biological remission and low BMI. Despite low BMI is usually associated with uncontrolled CD, particularly affecting the small bowel, a relatively low BMI (albeit far above the levels associated with malnutrition) could thus be associated with a lower systemic inflammatory burden, among the patients who are in clinical remission. The association between mesenteric fat and inflammation is well known and some authors have showed an association between higher BMI and bad prognosis in CD[11]. Furthermore the CRP production by mesenteric fat itself in the setting of CD may partly explain this observation[12]. Indeed, due to this local production, patients with increased mesenteric fat may more seldom achieve a normalization of their CRP concentration.

Factors independently associated with tissue remission were older older age, lower platelets count, absence of previous surgery, and the use of immunosuppressant. Older age and platelet count were also associated with biological remission. As highlighted here-above,

the association with a lower platelet count was already showed in the EXTEND trial, although in that study, an older age was associated with a lower rate of mucosal healing[7]. Several studies have shown the potential of immunosuppressants to achieve mucosal healing although it has been showed to be lower than with anti-TNF[13,14]. The fact that we found an association with immunosuppressant and not with anti-TNF may reflect a bias in the treatment of our patients. Most severe cases, particularly immunosuppressant refractory cases are treated with anti-TNF and the achievement of a tissue healing in those patients is difficult as highlighted in the EXTEND trial. On the contrary, the patients who remain under immunosuppressant treatment are most probably the good responders to these drugs. In those patients with an adequate response to immunosuppressants, the rate of mucosal healing has been showed around 75%[13].

Time to relapse was significantly longer in patients with biological remission as compared to patients without biological remission. This has already been published in several studies a while ago[15,16]. The elevation of a broad range of blood inflammatory markers, including CRP, IL6, sIL2R and ESR has been consistently associated with an increased risk of relapse. In the present study, biological remission also tended to be associated with a lower risk of surgery but not with a lower risk of hospitalization.

Time to relapse was also significantly longer in patients with tissue remission, as previously showed in the long-term follow up of controlled trials[3]. Tissue remission was also associated to a lower risk of surgery ($p = 0.04$) but not of hospitalization. This association with a lower rate of surgery was already found in a population-based study from Norway[4] and in another cohort of patients treated with infliximab in a tertiary referral centre[17].

Our study presents limitations. It is a retrospective monocentre study. Clinical remission or relapse were established either based on a HBI available in patients' notes or on a simple qualitative assessment by the clinician. Fecal calprotectin was not routinely used in those patients to confirm biological remission. No endoscopic or MRI score was prospectively calculated. The subgroup of patients being in biological remission but not in tissue remission was too small to draw any definitive conclusion about the added value of tissue remission over isolated biological remission to improve disease outcome. Nevertheless, the proportion of relapse in patients with biological but no tissue remission was numerically higher than in patients with combined biological and tissue remission. Likewise the impact of combined biological and tissue remission on the time-to-surgery seemed statistically more significant than the one of simple biological remission.

In conclusion, among patients in clinical remission, seen as outpatient in a referral centre, only one third is not in biological and/or tissue remission. Nevertheless, those patients are important to identify because they are at higher risk of relapse and more importantly, of surgery.

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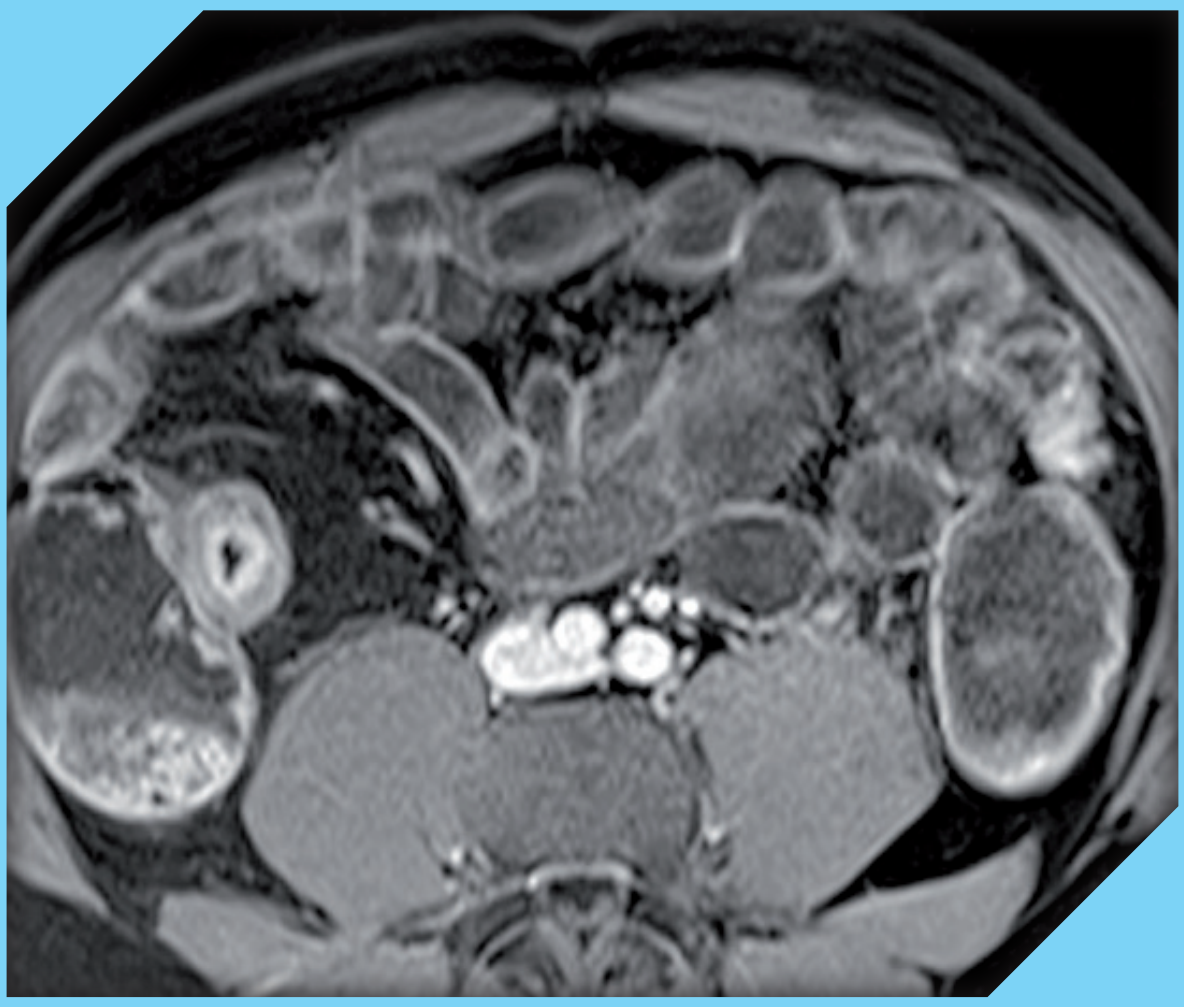
Article 4

Persisting signs of disease activity at Magnetic Resonance Enterocolonography predict clinical relapse and disease progression in quiescent Crohn's disease



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PERSISTING SIGNS OF DISEASE ACTIVITY AT MAGNETIC RESONANCE ENTEROCOLONOGRAPHY PREDICT CLINICAL RELAPSE AND DISEASE PROGRESSION IN QUIESCENT CROHN'S DISEASE

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Key words : *Crohn, Magnetic resonance enterocolonography, relapse, remission, calprotectin*

ABSTRACT

Introduction: Deep remission including clinical remission and tissue healing has been advocated as the therapeutic target in Crohn's disease. Yet, the definition of deep remission remains unclear.

The aim of this study was to assess the persisting lesions at magnetic resonance enterocolonography (MREC) in clinically quiescent Crohn's disease as well as their relapse predictive value.

Methods: we performed a prospective monocentre cohort study. We included patients with clinical remission. At baseline, these patients had blood tests, the measurement of fecal calprotectin and underwent a MREC. They were then followed up clinically for a minimum of 1 year. A relapse was defined by a HBI>4 with an increase of at least 3 points. Correlations between clinical, demographic, biological parameters and MREC signs were assessed as well as the time-to-relapse predictive value of the studied variables.

Results: Twenty seven patients were recruited. Fourteen out of 27 had persisting disease activity at MREC. MREC signs only partly correlated with biomarkers. Ten out of 27 patients relapsed over a median follow up of 25 months. In univariate analysis, relative contrast enhancement of the most affected segment (HR: 2.56; P=0.046), ulcers (HR: 12.5; P=0.039), fistulas (HR: 14.1; P=0.009) and target sign (HR: 3.63; P=0.049) were associated with relapse. In multivariate analysis, fistula was the only one.

Conclusions: Half of the patients with clinically quiescent Crohn's disease had persisting signs of disease activity at MREC. These signs predicted time-to-relapse.

INTRODUCTION

Crohn's disease is a progressive disease in a subset of patients, with tissue damage accumulating over time[1]. Therefore a treat to target approach has been advocated, aiming at tissue healing beyond the control of the symptoms[2,3]. The aim of this treat-to-target approach is to prevent the progression of the disease. The degree of tissue healing to be reached to achieve this aim is still unclear. In patients in clinical remission, the persistence of blood or stool markers of active inflammation is associated with an increased risk of relapse[4-6]. Likewise, the absence of mucosal healing has been associated with the risk of relapse, the risk of hospitalization, and the risk of surgical resection[7-9]. Hence a full mucosal healing has been advocated as the ultimate therapeutic objective and the guarantee that the disease would not progress. However, several data have come to qualify this assumption. First, in a large monocentre experience from Belgium, partial mucosal healing had a similar effect on the risk of subsequent abdominal surgery as a full healing suggesting that this kind of partial healing would be sufficient[9]. Second, in the specific situation of treatment de-escalation and more specifically infliximab withdrawal, full mucosal healing did not guarantee the absence of clinical relapse, which occurred in about one third of patients with mucosal healing[10]. Finally, the transmural nature of Crohn's disease has been re-emphasized, suggesting that an isolated mucosal healing with potentially remaining transmural inflammatory process not assessed by endoscopy may not mean full tissue healing[11]. From this point of view, magnetic resonance assessment of the bowel has become a standard to evaluate both activity of Crohn's disease[12,13] and tissue damage[14]. Specific scores have been proposed to assess disease activity[12,13], response to treatment[15] and tissue damage[14]. More specifically, for disease activity, the Magnetic Resonance Index of Activity (MaRIA) score has been shown to correlate well with endoscopic scores of severity[12,13]. However, the assessment of tissue healing by magnetic resonance, being transmural and even extraenteric, goes beyond the exclusive mucosal assessment of endoscopy.

The first aim of our study was to assess the degree of tissue healing observed at magnetic resonance enterocolonography (MREC) in patients with clinically quiescent Crohn's disease

and to correlate potential MREC signs and scores of persisting disease activity with blood and stool biomarkers. The second aim was to prospectively assess the time-to-relapse predictive value of these MREC signs and scores, in clinically quiescent Crohn's disease.

PATIENTS AND METHODS

We prospectively recruited patients with Crohn's disease seen as outpatient in our IBD clinic. The patients had to be in clinical remission, defined by a Harvey Bradshaw index ≤ 4, have a history of small bowel involvement by Crohn's disease, and give an informed consent for the study. Those patients underwent a MREC exploration, standard blood tests including blood cells counts, albumin and C-reactive protein measurement. The patients were also requested to bring a stool sample for fecal calprotectin measurement. Blood tests were performed using routine techniques. Fecal calprotectin was routinely measured using the Bühlmann ELISA (quantitative ELISA, range 30-1800 µg/g).

MREC was performed within one month of the bio-clinical assessment.

All examinations were performed using a 1.5 T MR Unit (Symphony; Siemens Medical Solutions, Erlangen, Germany). On the MRI table, patients were placed in the supine position for comfort reason (and subsequently better cooperation). Abdominal phased-array body coil was used to cover the entire field of the abdomino-pelvic region. A suitable repletion of the whole small intestine and colon was obtained by giving per os a mixture of Sorbitol and Methyl-Cellulose (about 1.4 L, as far as the patient can reasonably tolerate) and by administration of a lukewarm water enema about 1 L (according to patients' tolerance). Hypotonia was induced by administration of a peppermint oil capsule (Will Pharma) at the beginning of the oral intake and by IV injection of hyoscine butylbromide (Boehringer Ingelheim - 40 mg in two steps: the first one at the beginning of the examination, before the enema, and the second one just before the acquisition of the contrast-enhanced sequences).

The MR protocol included the following sequences: coronal True Fast Imaging with steady Precession (TRUE FISP) with Fat Saturation (FatSat), (slice thickness 5 mm, TR/TE 5.17/2.59 ms, field of view (FOV) 500 x 500 mm, flip angle 78°); coronal Volumetric Interpolated Breathold Examinations (VIBE) with FatSat before and after contrast injection (at the arterial (30 seconds) and portal (70 seconds) phases, (slice thickness 3 mm, TR/TE 4.30/1.44 ms, field of view 450 x 450 mm, flip angle 12°); coronal T2 Half-Fourier Single-shot Turbo spin-echo (HASTE) with and without FatSat, (slice thickness 5 mm, TR/TE 1310/90 ms, field of view 450 x 360 mm, flip angle 142°); axial T2 Half-Fourier Single-shot Turbo spin-echo (HASTE) without FatSat, (slice thickness 4 mm, TR/TE 1310/88 ms, field of view 340 x 272 mm, flip angle 142°); axial T1 VIBE "late" (about 5 minutes), (slice thickness 4 mm, TR/TE 5.22/2.42 ms, field of view 360 x 360 mm, flip angle 12°).

The enhancement was obtained by intra-venous injection of 0.2 ml/kg body weight of a gadolinium chelate (Gadobenate dimeglumine – Bracco) at a rate of 2 ml/sec.

All examinations were reviewed on a PACS (Agfa Healthcare) workstation by a single radiologist (PM) experienced in MREC. The MaRIA score was calculated[12]. A modified MaRIA score including two more segments (the jejunum and the proximal-mid ileum) was also calculated. The following parameters were evaluated in each segment : relative contrast enhancement (RCE) calculated according the following formula taking into account wall signal intensity (WSI) and standard noise (SD)[12]: RCE=((WSI postgadolinium– WSI pregadolinium)/(WSI pregadolinium))X100X(SD noise pregadolinium/SD noise postgadolinium); maximal bowel wall thickness; mural edema in T2 (hyperintensity of the bowel wall relative to the signal of the psoas muscle); presence of ulcers; presence of pseudo-polyps; presence of lymph nodes/adenomegalies (≥ 1 cm in the small diameter); presence of a bowel lumen dilatation (diameter > 4cm proximal to visible bowel wall lesions). The following parameters were assessed in the most affected segment: the target sign (layered enhancement of the bowel wall); the comb sign; presence of fistula(e); presence of a late "diffuse and homogeneous" parietal enhancement; presence of mesenteric infiltration; presence of abscess.

The patients were also classified depending on the MREC semiology in four categories: no persisting abnormality, parietal inflammation (presence of a submucosal edema on T2w sequences and a target sign), parietal and extraenteric signs of disease activity (presence of a submucosal edema on T2w sequences, a target sign and a comb sign), isolated extraenteric inflammation (comb sign).

The patients were then prospectively followed up for at least one year. A relapse was defined by a Harvey Bradshaw index >4 with an increase of at least 3 points as compared to baseline and the necessity to change the type or dosage of the medical treatment or the need for a surgical intervention. There was no further planned MREC in the follow-up.

No specific sample size calculation was made for this exploratory study. We planned to recruit around 30 patients within 6 months. Results are presented as medians and interquartile ranges for continuous variables and frequency tables for discrete variables. Some variables were logarithmically transformed to normalize distribution. Correlations between continuous variables were assessed by Spearman correlation test. Comparisons of means were made by the Student t test and the comparisons between discrete variables were made by Fisher's exact test. Time-to-clinical relapse predictive value of clinical, biological and MREC variables has been studied by univariate and multivariate Cox regression using stepwise selection. Results were considered as significant at the 5% level ($p<0.05$). Calculations were made with the SAS software version 9.3 (SAS Institute, Cary, NC, USA) and graphs with the S-Plus software version 8.1 (TIBCO Spotfire).

The protocol was reviewed and accepted by the ethics committee of Liège University Hospital on January the 24th of 2012.

RESULTS

Twenty-seven patients were recruited between March and September 2012. Baseline clinical, demographic and biological characteristics of the patients are presented in *Table 1*.

MREC signs and scores are presented in *Table 2*; 13/27 (48.1%) had no remaining sign of disease activity at MREC; 5/27 (18.5%) had only mural signs of disease activity; 8/27 (29.6%) had mural and extraenteric signs of disease activity; 1/27 (3.7%) had only extraenteric signs of disease activity.

Correlation between clinical and biological variables and the MREC signs and scores is shown in *table 3a and 3b*. Most significant correlations were found between MREC signs and platelet counts or fecal calprotectin, particularly for the MaRIA score and the segmental MaRIA score in the most severely affected segment *(figure 1)*.

All the patients were followed up till the study end in September 2014. Median follow-up was 25.1 months (IQR : 22.1 – 27.1). Ten out 27 patients relapsed with a median time to relapse of 8.9 months (IQR: 5.7-19.3).

Parameters associated with the time-to-relapse in univariate analysis are shown in *table 4.* In multivariate analysis, only the presence of a fistula at MREC was significantly associated with the time-to-relapse (HR= 14.1; 95%CI=1.9-101.9; p=0.009) *(figure 2)*.

Only two patients had to undergo surgical resection. The only factor associated with a shorter time-to-relapse in univariate analysis was the existence of MREC signs of fistula (HR=17.7; 95%CI= 1.1-294.7 P=0.045), while a lower blood hemoglobin (P=0.054) and a higher relative contrast enhancement in the most affected intestinal segment (P=0.053) were borderline for significance. The first operated patient had a fistula and a stricture in the terminal ileum at MREC; he was operated 10 months later and surgical resection specimen confirmed these lesions. The second operated patient had an ileal stricturing disease at MREC; she was operated 6 months later in a context of occlusion and surgical resection specimen confirmed the occlusive stricture of the terminal ileum.

DISCUSSION

Our study shows that half of the patients with clinically quiescent Crohn's disease have persisting signs of inflammation at MREC. These signs correlate only moderately to main biological signs of inflammation. It also shows the ability of MREC signs to predict time-to-relapse in those quiescent Crohn's disease patients. It finally suggests the superiority of these signs over classical stool and blood biomarkers for this prediction.

Table 1: patients characteristics

Male gender, n(%)		16 (59.3)
Age (yrs)	median (IQR)	31 (26-40)
Disease duration (yrs)	median (IQR)	7 (2-12)
Duration of remission (months)	Median (IQR)	15 (4-72)
Active smokers, n(%)		7 (25.9)
BMI (kg/m2)	median (IQR)	21.4 (19.8-23.2)
Age at diagnosis (Montreal), n(%)	A1	5 (18.5)
	A2	19 (70.4)
	A3	3 (11.1)
Location (Montreal), n(%)	L1	11 (40.7)
	L2	0 (0)
	L3	12 (44.4)
	L1+L4	2 (7.4)
	L3+L4	2 (7.4)
Behaviour (Montreal), n(%)	B1	13 (48.1)
	B2	9 (33.3)
	B3	5 (18.5)
Perianal lesions, n(%)		3 (11.1)
Harvey Bradshaw Index, n(%)	0	5 (18.5)
	1	7 (25.9)
	2	1 (3.7)
	3	7 (25.9)
	4	7 (25.9)
CRP (mg/L)	median (IQR)	2.1 (0.9-4.6)
Fecal calprotectin (µg/g)*	median (IQR)	300 (92-470)
Albumin (g/dl)**	median (IQR)	45 (41.5-47.0)
Platelet count (109/L)	median (IQR)	288 (260-328)
Hemoglobin (g/L)	median (IQR)	14 (13.3-14.8)
Treatment, n(%)	mesalazine	5 (18.5)
	steroids	0 (0)
	immunosuppressant	7 (25.9)
	anti-TNF	15 (55.6)
	none	5 (18.5)

** n=13; ** n=24*

Montreal classification : L1=ileal, L2=colonic, L3=ileocolonic, L4=upperGI tract ; B1=non structuring/non penetrating, B2=stricturing, B3=penetrating; A1= <17years, A2=18-40years, A3= >40 years.

Table 2: MREC signs and measurements

Bowel wall edema in T2, n(%)	10 (37)
Target sign, n(%)	10 (37)
Ulcer, n(%)	1 (3.7)
Late contrast enhancement, n(%)	21 (77.8)
Bowel lumen dilatation, n(%)*	1 (3.7)
Fistula, n(%)	2 (7.4)
Abcess, n(%)	0 (0)
Comb sign, n(%)	9 (33.3)
Mesenteric infiltration, n(%)	4 (14.8)
Mesenteric adenomegalies, n(%)**	5 (18.5)
Relative contrast enhancement, median (IQR)***	106 (76.5-144)
Bowel wall thickness (mm), median (IQR)	6 (4-9)
MaRIA score, median (IQR)	38.5 (34-48.5)
Modified MaRIA score, median (IQR)****	52.6 (45.7-60.7)
Maximal segmental MaRIA score, median (IQR)*****	10.8 (8.1-21.4)

** presence of a bowel lumen diameter >4cm upstream to the lesions*

*** presence of lymph nodes > 1 cm*

**** RCE was calculated according the following formula: RCE=((WSI postgadolinium–WSI pregadolinium)/(WSI pregadolinium))X100X(SD noise pregadolinium/SD noise postgadolinium)*

***** calculated as the MaRIA score but also including a proximal and mid-ileal segment and a jejunal segment*

****** Segmental MaRIA score in the most affected segment*

Table 3b: Clinical and biological variables according to MREC measurements (continuous variables).

	HBI	BMI	dis. dur. (yrs)	CRP (mg/l)	Fec. calpro. (µg/g)*	Album. (g/L)**	Hemo-gl.(g/L)	Platelet (109/L)
MaRIA score	-0.35 (p=0.07)	0.35 (p=0.07)	-0.14 (p=0.50)	0.11 (p=0.59)	**0.59 (p=0.03)**	-0.16 (p=0.46)	-0.02 (p=0.92)	**0.51 (p=0.006)**
Modified MaRIA score	**-0.44 (p=0.02)**	0.32 (p=0.10)	-0.04 (p=0.84)	0.08 (p=0.69)	**0.66 (p=0.01)**	-0.26 (p=0.21)	-0.12 (p=0.56)	**0.53 (p=0.005)**
Maximal Segmental MaRIA score	-0.28 (p=0.16)	0.29 (p=0.15)	0.09 (p=0.65)	0.11 (p=0.58)	**0.66 (p=0.01)**	-0.14 (p=0.53)	-0.15 (p=0.46)	**0.55 (p=0.003)**
Maximal relative contrast enhancement	-0.24 (p=0.23)	0.23 (p=0.24)	0.01 (p=0.96)	0.08 (p=0.68)	0.52 (p=0.07)	-0.24 (p=0.25)	-0.27 (p=0.17)	**0.39 (p=0.04)**
Bowel wall thickeness	-0.16 (p=0.43)	0.16 (p=0.42)	0.09 (p=0.64)	0.14 (p=0.48)	**0.64 (p=0.02)**	-0.20 (p=0.35)	-0.24 (p=0.23)	**0.56 (p=0.002)**

**n=13; **n=24*

Table 3a. Clinical and biological variables according to MREC signs (expressed as discrete variables).

		HBI	BMI	dis. dur. (yrs)	CRP (mg/l)	Fec. calpro (µg/g)	Album. (g/L)	Hemogl. (g/L)	Platelets (109/L)
Bowel wall edema in T2	Yes (n=10)	1 (1-3)	22.9 (21.8-25.3)	8 (5-12)	2.4 (1-4.6)	600 (300-600)	43.5 (39.5-47.5)	14 (11.8-14.8)	323 (288-336)
	No (n=17)	3 (1-4)	20.5 (19.8-21.9)	7 (2-15)	2 (0.9-3.4)	147 (71-372)	45.5 (43-47)	14 (13.3-14.6)	280 (255-293)
	p value	*0.093*	*0.13*	*0.81*	*0.91*	**0.024**	*0.42*	*0.85*	**0.023**
Target sign	Yes (n=10)	3 (1-3)	22.5 (19.8-29.9)	10.5 (7-12)	2.6 (1.5-5.2)	385 (256-600)	41 (32-47)	13.7 (11.8-15)	311 (285-336)
	No (n=17)	1 (0-4)	20.6 (19.9-22.5)	6 (2-11)	2 (0.7-2.7)	92 (62-434)	45 (44-47)	14.1 (13.3-14.6)	284 (255-293)
	p value	0.37	0.071	0.74	0.64	0.15	**0.037**	0.66	**0.055**
Ulcer	Yes (n=1)	1 (1-1)	18.3 (18.3-18.3)	12 (12-12)	2.5 (2.5-2.5)	600 (600-600)	32 (32-32)	11.8 (11.8-11.8)	318 (318-318)
	No (n=26)	3 (1-4)	21.6 (19.9-23.2)	7 (2-12)	2.1 (0.9-4.6)	278 (86-452)	45 (42-47)	14.1 (13.3-14.8)	287 (260-328)
	p value	0.46	0.31	0.57	0.8	0.17	**0.008**	0.19	0.65
Late contrast enhancement	Yes (=21)	3 (1-4)	21.9 (20.1-23.8)	7 (4-13)	2.1 (0.9-4.6)	256 (92-309)	45 (43-48)	14.1 (13.5-15.5)	285 (255-328)
	No (n=6)	1 (1-3)	20.2 (18.3-20.6)	8.5 (1-12)	2 (1.5-2.5)	452 (240-535)	42 (40-46)	12.6 (11-13.5)	302 (293-318)
	p value	0.39	0.095	0.56	0.43	0.41	0.18	**0.007**	0.45
Bowel lumen dilatation*	Yes (n=1)	3 (3-3)	29.9 (29.9-29.9)	7 (7-7)	0.2 (0.2-0.2)	NA	NA	15.3 (15.3-15.3)	334 (334-334)
	No (n=26)	2.5 (1-4)	21.1 (19.8-23.2)	7 (2-12)	2.1 (1-4.6)	300 (92-470)	45 (41.5-47)	13.9 (13.3-14.6)	287 (260-318)
	p value	0.58	0.046	0.81	0.69	NA	NA	0.25	0.5
Fistula	Yes (n=2)	2 (1-3)	19 (18.3-19.7)	12.5 (12-13)	3.6 (2.5-4.6)	428 (256-600)	41 (32-50)	13.4 (11.8-15)	366 (318-414)
	No (n=25)	3 (1-4)	21.8 (20.1-23.2)	7 (2-12)	2 (0.9-3.4)	300 (80-470)	45 (42-47)	14 (13.3-14.6)	286 (260-307)
	p value	0.89	0.23	0.34	0.79	0.42	0.37	0.79	0.095
Comb sign	Yes (9)	2 (1-3)	22.6 (19.7-23.2)	9 (7-12)	2.5 (2-4.6)	600 (470-600)	43 (38-46)	14 (11.8-14.5)	318 (300-334)
	No (18)	3 (1-4)	21.1 (20.1-22.5)	6.5 (2-12)	1.8 (0.7-3.4)	147 (71-304)	46 (44-47)	14 (13.3-14.8)	282 (255-293)
	p value	0.55	0.58	0.76	0.95	**0.003**	0.19	0.5	**0.035**
Mesenteric infiltration	Yes (n=4)	2 (1-4)	19.9 (18.7-22)	12 (11.5-13.5)	2.3 (1.8-3.9)	331 (62-600)	39 (32-47.5)	14 (12.7-14.8)	294 (285-311)
	No (n=23)	3 (1-4)	21.8 (19.9-23.8)	7 (2-12)	2 (0.7-4.6)	300 (92-470)	45 (42.5-47)	14 (13.3-14.7)	288 (255-334)
	p value	0.89	0.29	0.16	0.62	0.89	**0.051**	0.97	0.73
Mesenteric adenomega-lies**	Yes (n=5)	3 (2-3)	22.5 (19.7-23.2)	7 (2-9)	2.7 (2.3-4.6)	256 (80-600)	41 (41-44)	13.4 (11.8-14.6)	286 (202-414)
	No (n=22)	2 (1-4)	21.1 (19.9-23.2)	7 (4-12)	2 (0.7-3.4)	305 (92-470)	46 (43-47)	14.1 (13.3-14.8)	288 (262-318)
	p value	0.69	0.63	0.41	0.97	1.0	0.53	0.49	0.54

** presence of a bowel lumen diameter >4cm upstream to the lesions*

*** presence of lymph nodes > 1 cm*

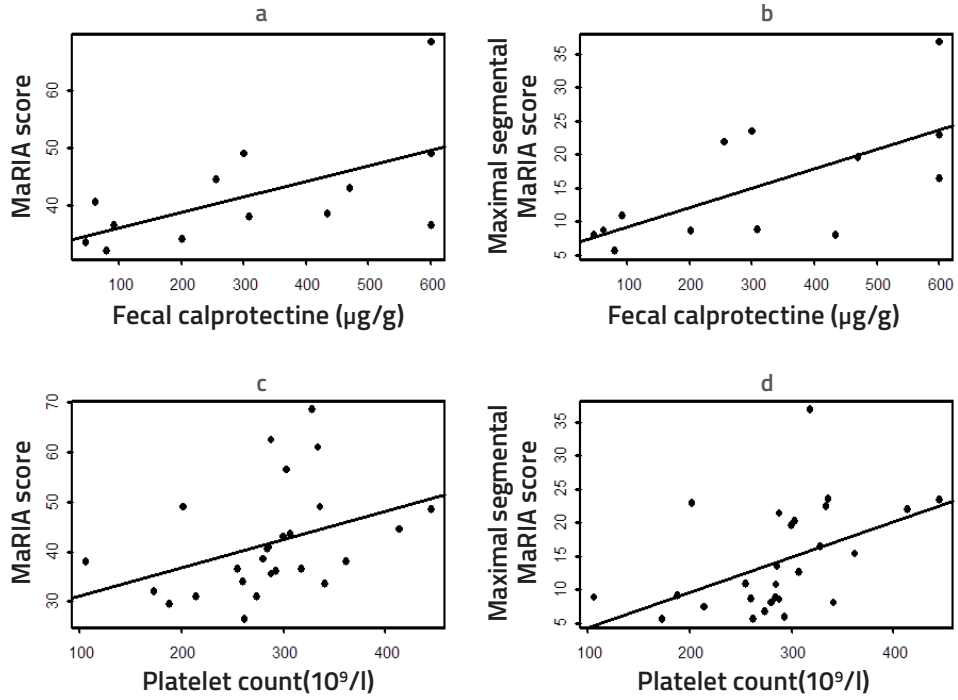

Fig. 1: *(1a) Correlation between fecal calprotectin and MaRIA score (r=0.59; p=0.03); (1b) fecal calprotectin and segmental MaRIA in the most affected segment (r=0.66; p=0.01); (1c) platelet count and MaRIA score (r=0.51; p=0.006); (1d) platelet count and segmental MaRIA in the most affected segment (r=0.55; p=0.003).*

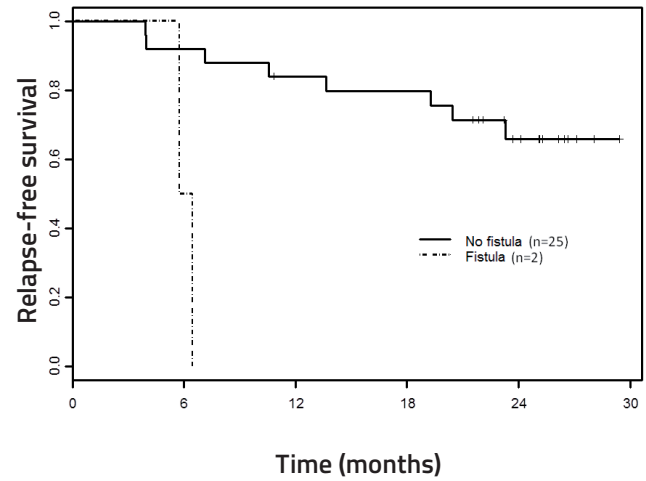

Fig. 2: *Time-to relapse according to the presence of an intra-abdominal fistula at MR entero-colonography (HR= 14.1; 95%CI=1.9-101.9; p=0.009).*

Table 4 : Time-to-relapse predictive value of the studied parameters in univariate analysis. Only parameters with a p value <0.1 are showed. Fecal calprotectin and MaRIA score are also showed although their p value is >0.1.

	Hazard Ratio	95%CI	p Value
CRP (logarithm)	1.61	0.97-2.67	0.064
Platelet count	1.01	0.99-1.02	0.085
Fecal calprotectin	1.001	0.99-1.004	0.74
Parietal and extraenteric signs*	3.6	0.89-14.5	0.072
MaRIA (logarithm)	0.85	0.07-11.20	0.90
segmental maximal MaRIA** (logarithm)	3.04	0.81-11.45	0.10
Maximal relative contrast enhancement	2.56	**1.02-6.45**	**0.046**
Ulcer	12.5	**1.13-138**	**0.039**
Target sign	3.63	**1.01-13.1**	**0.049**
Comb sign	3.13	0.88-11.2	0.078
Fistula	14.1	**1.95-102**	**0.009**

**defined as mucosal enhancement, submucosal edema and a comb sign.*

*** MaRIA in the most affected segment.*

The first objective of the present study was to better characterize the nature of the persisting inflammatory process which may be disclosed by MREC in clinically quiescent Crohn's disease. Our study population includes patients with different types of treatment and disease history and represents thus a range of what can be observed in routine practice. Half of the patients had remaining signs of disease activity at MREC. This discrepancy between clinical activity mainly based on subjective symptoms evaluation and more objective signs of inflammation has already been shown for blood and stool biomarkers[4-6] as well as endoscopy[16,17]. A good correlation between endoscopic and MRI assessment of disease activity has already been shown[12,13]. The main advantage of MRI is to enable full gastro-intestinal tract assessment in only one single procedure. In the present study 5/27 patients presented lesions in segments which are out of reach of classical ileocolonoscopy. Biomarkers are less invasive and cheaper than endoscopy or MRI but their correlation with mucosal healing at endoscopy has been shown to be variable[18,19]. The same is shown in the present study: there was no significant correlation between the most broadly used biomarker, CRP, and most of the MREC signs of disease activity. The absence of correlation with signs of inflammation in the bowel wall had already been shown with CT scanner[20]. However, a significant correlation was found with extraenteric signs of inflammation including the comb sign and creeping fat. In the present study, only a minority (9/27) of the patients had extraenteric signs of disease activity, which may have led to a lack of power to show this association. Among biomarkers, only platelet count and fecal calprotectin significantly cor-

related with MREC signs of disease activity. These markers have already been shown to be reliable markers of tissue healing at endoscopy[21, 22] and this is therefore not surprising to find a good correlation with the MaRIA score, which was consistently showed to correlate with endoscopic score of activity[12,13]. In the present study, fecal calprotectin and platelet count correlated both with bowel wall and extraenteric signs of disease activity. This is not surprising either since almost all the patients (8/9) with remaining extraenteric signs of disease activity (comb sign and/or mesenteric infiltration) at MREC had also signs of activity in the bowel wall (T2 edema and/or target sign).

The second objective of our study was to assess the relapse predictive value of MREC signs in clinically quiescent Crohn's disease. A relapse predictive value has already been shown for several blood markers, including CRP, but also erythrocytes sedimentation rate, cytokines such as interleukin-6 or the soluble receptor of interleukin-2[4-6]. An increased intestinal permeability has also been associated with this increased risk of relapse[23]. More recently, attention has been focusing on stool markers, particularly fecal calprotectin. Fecal calprotectin appeared superior to classical blood markers to predict relapse[6]. At the same time, fecal calprotectin also correlated better with endoscopic scores of severity[19]. Overall, these elevated biomarkers, and particularly fecal calprotectin, have thus been interpreted as being surrogate markers of incomplete disease control, leading to a risk of disease relapse and beyond that, disease progression. Meanwhile treatment strategies have evolved towards a treat-to-target approach, the treatment being optimized according to the results of the monitoring of disease activity using objective markers[2,3]. In this setting, MREC presents many theoretical advantages in the assessment of Crohn's disease patients. It allows, in one single procedure, the assessment of the whole intestine and the assessment of both the bowel wall and extraenteric inflammatory process. In a retrospective study, we suggested that among patients in clinical remission, the subgroup who had endoscopic mucosal healing or a normalization of magnetic resonance imaging of the intestine had a lower risk of relapse and a lower risk of abdominal surgery[24]. In the present prospective study we confirm that MREC is able to predict time-to-relapse in clinically quiescent Crohn's disease. Although only few surgical events were observed, our results suggest that MREC can also predict the risk of surgical resection and thus the tissue damage progression. Isolated specific signs were better predictors than more global assessment like differentiating between normal and abnormal, or the global and modified MaRIA. The MaRIA score, best associated with endoscopic scores of severity, and assessing the activity of the disease at the mucosal level was not a predictor of the time-to-relapse. This may be linked to the fact that it is not the global mean severity of the disease which is important here but rather the severity of focal lesions, and even more specifically specific signs associated with this severity, i.e. intensity of contrast enhancement, the presence of a target sign, a mucosal ulcer or a fistula, which was in multivariate analysis the only element selected. Although this has to be interpreted with caution due to the fact that only two patients had fistula, this kind of lesion has already recently been shown to predict the risk of surgery in active Crohn's disease patients[25].

The signs that best predicted the time-to-relapse were not only mucosal signs, which could also be assessed by endoscopy, but also transmural signs, including bowel wall edema and fistula, which are more difficult to assess by endoscopy. Importantly, in the present study, these MR signs were better predictors of time-to-relapse than biomarkers. CRP and platelets count were only borderline significant for relapse prediction and fecal calprotectin was not. This may be linked to a lack of power, particularly for fecal calprotectin (significant proportion of missing values), since these markers have previously clearly been shown to be associated with the risk of relapse. On the other hand, it emphasizes the strength of MR signs in this prediction, already statistically significant in a relatively small set of patients.

Our study has strengths and weaknesses. The main strengths are its originality, its prospective nature and the careful assessment of the MR images by a single experienced radiologist. The main weaknesses are the relatively small sample size, but which was sufficient to demonstrate the value of MREC in the assessment of clinically quiescent Crohn's disease, and the fact that half of the patients did not bring back a stool sample for fecal calprotectin assessment. This particularly small sample size for fecal calprotectin may also explain why the median value is a bit higher than previously reported in the literature for Crohn's disease patients in remission. However, this assessment was not a main aim of our study. Another weakness is the fact that the baseline MREC could have influenced the management of the patients and thus influenced the outcome. However, this was not the case as no change in treatment was performed within three months after this exploration. Finally, the confirmation of the clinical relapse with objective markers of activity including a new MREC would have helped to strengthen the potential predictive value of this exploration.

In conclusion, in patient with clinically quiescent Crohn's disease, MR signs of disease activity (both extraenteric and in the bowel wall) may persist in a subset of patients and usually coexist. These signs such as the presence of a target sign and the relative contrast enhancement in the bowel wall as well as the presence of mucosal ulcers and the presence of enteric fistula are associated with shorter time to relapse in patients with clinically quiescent Crohn's disease. This association was stronger than for classically used blood or stool biomarkers. These predictors should be validated in a larger independent cohort and an intervention study should be performed to evaluate if a treatment optimization is able to decrease the risk of relapse and disease progression in this situation.

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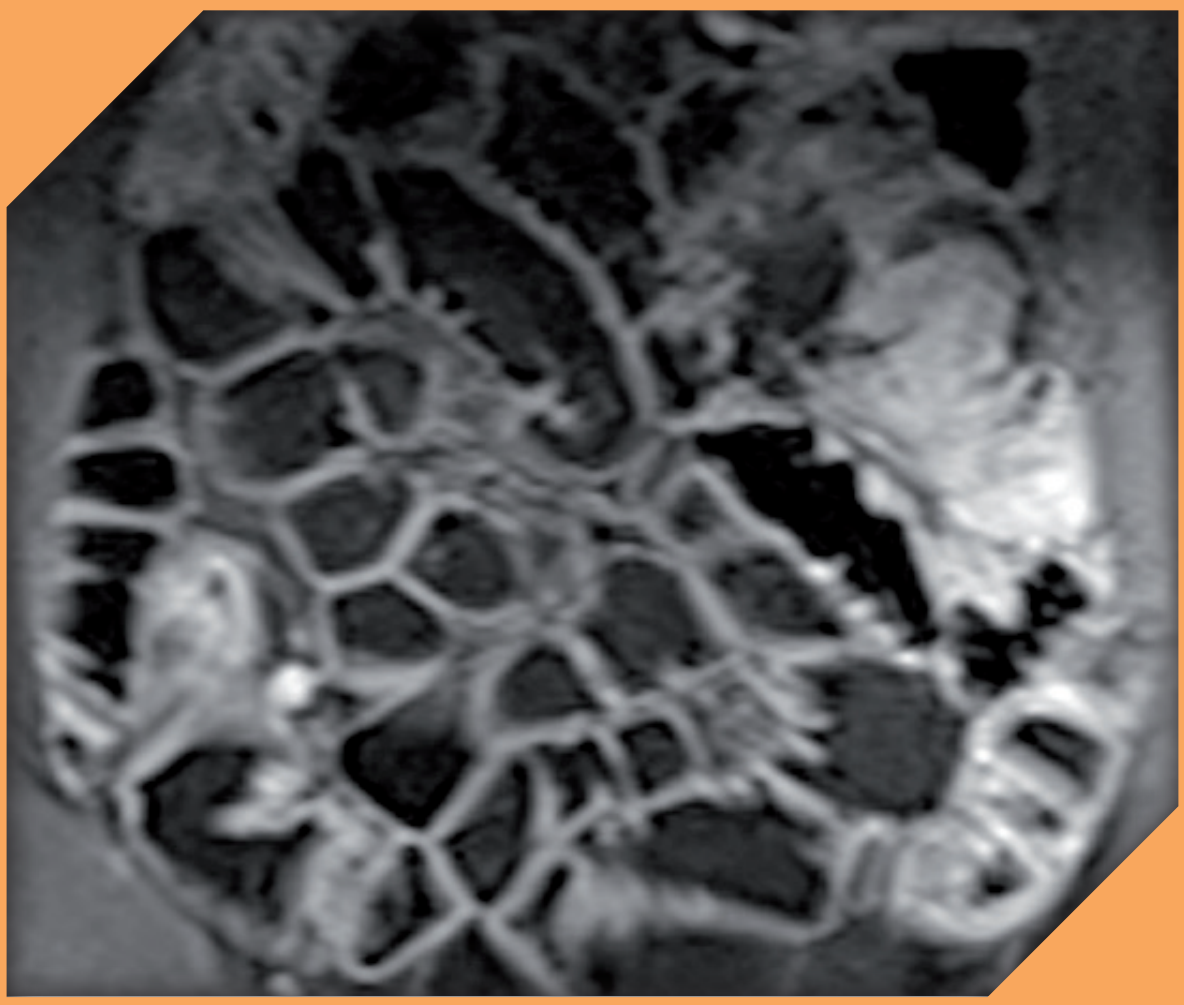
DISCUSSION GENERALE & CONCLUSION



L'IRM, longtemps considérée comme un examen relativement peu fiable pour l'exploration du tube digestif en raison d'une résolution temporelle et spatiale limitée, a bénéficié, depuis une dizaine d'années, d'avancées technologiques importantes. L'optimisation des séquences d'acquisition, l'absence de nocivité démontrée de la technique (en dehors d'une exposition à de hauts champs), en particulier l'absence d'irradiation, et l'amélioration des techniques de réplétion du tube digestif (imprégnation séquentielle per os/hypotonie) en font, à l'heure actuelle, un mode d'exploration incontournable dans la mise au point et le suivi de la maladie de Crohn[34, 41, 47, 57-65].

Le potentiel de détection et de définition des anomalies rencontrées dans cette pathologie, les progrès dans leur analyse morphologique (actuelle) et fonctionnelle (à venir) justifient notre intérêt et notre investissement pour et dans cette technique.

La corrélation de certains paramètres (voir introduction) est bien établie avec l'activité de la maladie.

Au fil de cette analyse, nous allons successivement envisager et discuter de l'impact de l'IRM dans :

- la réponse thérapeutique;
- le dommage tissulaire;
- la notion de rémission profonde;
- la prédiction de la récidive;

en utilisant tout le potentiel exploratoire trans- et extramural de la technique.

Le premier article étudie l'influence du traitement par Infliximab sur les lésions transmurales.

Même si la résolution complète des lésions s'est révélée un phénomène rare et bien que la majorité des patients ait gardé des signes d'une activité partielle et une absence d'amélioration des symptômes (sub-)obstructifs 26 semaines après le début du traitement, il s'agit de la première série prospective démontrant par IRM l'efficacité de l'Infliximab sur l'atteinte transmurale.

L' absence de régression de la composante obstructive de la symptomatologie pourrait s'expliquer par la présence d'une composante lésionnelle fibreuse. Par ailleurs, on peut aussi spéculer sur le fait qu'un contrôle plus tardif qu'à la semaine 26 aurait pu montrer des signes plus francs de régression. Il est également important de noter que l'amélioration clinique (sur la base des CDAI et HBI)[66, 67] et de la CRP ont été plus rapides que l'amélioration de l'atteinte transmurale.

Les limites de cette étude sont principalement le petit nombre de patients, l'absence de corrélation à des données endoscopiques (et donc à l'atteinte muqueuse), l'utilisation d'un

score non validé (étude commencée avant l'établissement du score de MaRIA) et non corrélé à la CRP, la durée relativement courte du suivi ne permettant pas l'évaluation de la signification des lésions résiduelles à la semaine 26 (l'analyse de la signification de ces lésions résiduelles à l'IRM chez des patients en rémission clinique sera d'ailleurs l'objet de la dernière partie de notre travail); en outre, la durée moyenne de la maladie était relativement longue, expliquant l'importance des lésions fibrosantes réagissant peu au traitement.

Néanmoins, l'étude démontre une amélioration des composantes transmurale et extramurale de l'atteinte, même si des signes d'activité et d'obstruction persistent en IRM chez des patients en rémission clinique.

La définition du rôle de l'IRM dans l'évaluation de la réponse au traitement, notamment par anti-TNF, reste donc à préciser sur la base d'études incluant des populations plus importantes et de durée plus longue afin de permettre, d'une part, de vérifier de façon plus approfondie l'impact thérapeutique de l'Infliximab sur l'atteinte transmurale et, d'autre part, de différencier l'activité du dommage tissulaire.

C'est l'objectif du deuxième article de ce travail, qui vise à définir un outil de quantification du dommage tissulaire (index de Lémann), afin d'évaluer l'évolution de la maladie sur le long terme alors que les index actuels (cliniques ,biologiques et morphologiques - cfr. première partie de notre travail) ne mesurent que l'activité à un moment précis.

Ce dommage progressif et cumulatif inclut les lésions sténosantes, les lésions pénétrantes et les recours à la chirurgie de résection[54, 68].

L'analyse du dommage a été effectuée de façon systématique, segment par segment, puis organe par organe, pour obtenir finalement un score global bien corrélé à l'évaluation de la maladie appréciée par des investigateurs, basée sur leur expérience clinique essentiellement. L'index construit repose sur la gradation de lésions sténosantes et pénétrantes ainsi que des résections aux différents niveaux du tube digestif. La valeur attribuée à ces grades ainsi que leur pondération et leur addition conduisent à la valeur globale de l'index.

L'index de Lémann augmente avec la durée de la maladie (accumulation de dommages irréversibles) et est indépendant de l'activité clinique à un temps donné. Ces deux caractéristiques sont en accord avec la logique de construction de cet indice: le but n'est pas d'évaluer l'activité de la maladie à un moment donné, mais de quantifier le dommage tissulaire s'accumulant au fil du temps.

L'index de Lémann, malgré les limitations de ce travail (notamment la division arbitraire par segments et le recueil de petits échantillons en ce qui concerne le tube digestif supérieur), sa reproductibilité imparfaite en raison de son caractère novateur (pas suffisamment de pratique)[69] et des variations inter-observateurs (nécessitant une validation croisée)[70 - 72]

n'en devient pas moins le premier outil de mesure du dommage tissulaire cumulé. S'il n'est pas applicable partout (procédure à apprendre), il est le premier à pouvoir mesurer l'impact à long terme de la maladie de Crohn et celui des différentes stratégies thérapeutiques sur son devenir.

Il devrait aussi permettre d'identifier des paramètres associés à un risque de progression rapide. Dans sa construction, l'index de Lémann s'est voulu indépendant des outils utilisés pour le calculer. Il n'est donc pas exclu qu'une validation soit recherchée pour un index calculé uniquement sur la base de l'IRM, qui a la capacité de visualiser en un seul examen l'entièreté du tractus digestif et même, si les acquisitions sont adaptées, la région péri-anale. Ceci est imaginable dans la mesure où les lésions utilisées pour la gradation du dommage dans les segments évalués par l'endoscopie sont les lésions sténosantes, les ulcères et les fistules, autant de lésions pouvant aussi être évaluées par l'IRM (à l'exception des ulcérations superficielles mais qui n'ont qu'une très faible répercussion sur l'index de Lémann).

Les notions d'activité de la maladie et de dommage tissulaire nous amènent à considérer la définition même de ce que devrait être la rémission dans la maladie de Crohn. C'est l'activité de la maladie qui conduit au dommage tissulaire, mais c'est le dommage tissulaire qui, en plus de son impact possible sur les symptômes, va entrainer l'altération fonctionnelle irréversible de l'appareil digestif et par là consacrer et fixer les conséquences de la pathologie sur le long terme pour le patient. La rémission de la maladie de Crohn devrait donc être associée non seulement à un contrôle des symptômes cliniques du patient mais aussi, et plus encore, à un contrôle de l'activité inflammatoire de la maladie permettant d'annuler ou de ralentir la progression du dommage tissulaire.

Il n'y a pas de corrélation satisfaisante entre rémissions clinique et biologique et cicatrisation intestinale (muqueuse au sens endoscopique du terme)[55].

Qui plus est, on observe régulièrement la persistance d'anomalies endoscopiques et/ou d'imagerie lors des périodes de rémission clinique. Comme évoqué plus haut, ces lésions peuvent être en rapport avec un risque accru de récidive et de progression de la maladie (accroissement du dommage tissulaire)[73-75].

Le concept nouveau de rémission profonde doit donc intéresser non seulement l'état clinique et biologique, mais également le status lésionnel (cicatrisation muqueuse à l'heure actuelle). Cette notion revêt une importance particulière par son influence potentielle sur la gestion du traitement, en particulier le timing d'utilisation des traitements anti-TNF, et sur le monitoring et l'évaluation de la réponse soutenue au traitement.

En effet, il apparait que l'usage des anti-TNF est en général réservé à des patients souffrant d'une maladie évoluant depuis longtemps alors qu' il est probable que leur emploi plus précoce puisse infléchir le cours de la maladie et permettre au malade d'atteindre plus sûrement et plus fréquemment le stade de rémission profonde[76]. En outre, une évaluation mor-

phologique apparait nécessaire pour confirmer la rémission clinique et s'assurer du contrôle suffisant de la maladie au niveau tissulaire.

Actuellement toutefois, il reste beaucoup d'inconnues pour pouvoir définir et atteindre cet objectif de rémission profonde dans la pratique de routine. Le niveau de contrôle de l'inflammation tissulaire et de cicatrisation à obtenir pour éviter la progression du dommage tissulaire n'est pas déterminé. On ne connait pas la proportion de patients qui atteignent cet état en routine clinique avec les stratégies thérapeutiques actuelles, les facteurs qui y sont associés, son influence sur le devenir des patients et l'évolution de leur maladie à moyen ou long terme.

En outre, si la cicatrisation muqueuse peut être appréciée endoscopiquement, au moins partiellement, la notion de cicatrisation pariétale ne saurait être appréciée que par une technique englobant l'ensemble de la paroi, en l'occurrence l'IRM.

Apporter des éléments de réponse à ces questions constitue la 3ème et la 4ème partie de notre travail.

Le troisième article, rétrospectif, a tenté d'évaluer la prévalence de la rémission profonde et d'examiner la possible corrélation entre cette rémission et l'évolution de la maladie. La rémission biologique était définie par une CRP normale, la rémission tissulaire par la disparition des signes d'activité de la maladie à l'IRM et/ou l'absence d'ulcère en endoscopie.

Dans le groupe de patients étudié (ambulatoires, en rémission clinique), deux tiers étaient en rémission biologique et/ou tissulaire.

Cette rémission était associée à une meilleure évolution de la maladie.

La rémission biologique était associée à un âge plus avancé et un BMI bas, un faible taux de plaquettes et une hémoglobine haute ainsi qu'à un risque plus faible d'évolution ou de récidive et à une cicatrisation muqueuse[76, 77].

La rémission tissulaire était associée à un âge plus important, des plaquettes basses et l'absence d'antécédents chirurgicaux ainsi qu'à un traitement par immunosuppresseurs. Cet aspect n'est pas retrouvé avec les anti-TNF probablement à cause d'un biais. La raison en est que ce sont les formes les plus sévères et les plus évolutives qui sont traitées par anti-TNF. Dans cette population, il y a donc un taux de récidive plus important puisqu'il s'agit de formes plus graves.

La rémission profonde (biologique et tissulaire - évaluée notamment à l'IRM) s'est révélée associée à un délai de rechute plus long et à une diminution du risque chirurgical[74-78].

Cette étude met donc en évidence un élément important: un tiers des patients en rémission clinique n'est pas en rémission biologique et/ou tissulaire. Ces patients présentent un haut risque de récidive et/ou d'évolution vers la chirurgie et il est donc important de pouvoir les identifier.

Les limites principales de cette étude résident dans son caractère rétrospectif et monocentrique. Le caractère rétrospectif n'a notamment pas permis une analyse fine des lésions IRM les plus discriminantes pour évaluer le risque de rechute ou de progression de la maladie.

C'est l'objet du quatrième article, dernière partie de ce travail, qui s'est attaché à étudier la valeur prédictive de récidive des signes IRM chez les patients en rémission de leur maladie de Crohn.

L'objectif thérapeutique actuel dans la maladie de Crohn est la cicatrisation muqueuse afin de limiter le dommage tissulaire et de prévenir la progression de la maladie[79, 80].

Mais, comme évoqué plus haut, le degré de cicatrisation à atteindre n'est pas clairement établi et si l'absence de cicatrisation muqueuse (au sens endoscopique)[73, 78, 81] et la persistance de marqueurs biologiques de l'inflammation sont associés à un plus grand risque de récidive[82-84], certaines données atténuent ces affirmations: une étude récente suggère qu'une cicatrisation partielle serait suffisante[78] et dans le contexte d'une désescalade thérapeutique, on sait que la cicatrisation muqueuse complète ne garantit pas de l'absence d'une récidive que l'on retrouve chez un tiers des patients ayant obtenu une cicatrisation iléo-colique totale[75].

Cela nous amène donc à considérer l'atteinte pariétale dans son ensemble et non seulement l'atteinte muqueuse seule : il est possible que ce que l'on considère endoscopiquement comme une cicatrisation complète n'en soit pas une[53].

À ce titre, l'IRM est devenue un moyen intéressant d'évaluation de l'activité et du dommage tissulaire dans la maladie de Crohn[34, 41].

Le premier but de ce dernier travail est d'évaluer le degré de cicatrisation muqueuse observé à l'ecMR et de corréler ces signes et scores IRM d'activité pariétale persistante aux marqueurs biologiques.

Le deuxième but est d'évaluer la valeur prédictive de ces signes et scores sur le délai de récidive chez des patients quiescents.

En ce qui concerne le premier but, nous avons constaté que la moitié des patients cliniquement quiescents présentaient toujours des signes d'activité de la maladie à l'ecMR. Cette discordance a aussi été démontrée dans d'autres études pour les biomarqueurs[82-84] et pour l'endoscopie[55, 56].

Par contre, si nous n'avons pas mis en évidence une corrélation robuste entre biomarqueurs et signes pariétaux d'activité à l'ecMR (ce qui avait déjà été le cas avec le CT)[54], nous avons trouvé une corrélation satisfaisante avec les signes d'atteinte extrapariétale; mais cela ne concernait qu'un tiers des patients dont la majorité présentait par ailleurs également des signes d'atteinte pariétale.

Parmi les marqueurs, seules les plaquettes et la calprotectine fécale présentaient une corrélation significative mais imparfaite avec les signes ecMR d'activité, comme ils le sont déjà pour l'endoscopie[15, 76], et il n'est donc pas surprenant qu'ils le soient aussi avec le score IRM de MaRIA qui a été construit pour obtenir une corrélation maximale avec les scores endoscopiques d'activité de la maladie de Crohn[29, 41].

En ce qui concerne le deuxième but, la calprotectine fécale s'est révélée, jusqu'à présent, comme le marqueur le plus fiable pour prédire la récidive[84], et présente la meilleure corrélation avec les scores endoscopiques[85]. C'est extrêmement important dans le contexte de l'approche thérapeutique actuelle, visant à obtenir une rémission profonde, car cela permettrait d'en suivre l'obtention.

Comme nous l'avions suggéré dans le travail précédent, nous confirmons l'hypothèse selon laquelle l'ecMR est aussi capable de prédire le délai de récidive et même, sous réserve d'une population réduite, le risque chirurgical et donc la progression du dommage tissulaire.

De façon intéressante, il semble que ce soit plutôt la sévérité de lésions focales que la sévérité « globale » de l'atteinte qui soit importante, ce qui explique la faible capacité de prédiction du score de MaRIA (même segmentaire) reflet d'une activité inflammatoire tissulaire générale à un moment donné.

Plus spécifiquement, les signes suivants:

- intensité du rehaussement pariétal;
- stratification du rehaussement pariétal (signe de la cible);
- ulcère(s);
- fistule(s);

se sont révélés comme les meilleurs prédicteurs du délai de récidive, supérieurs même aux biomarqueurs (la corrélation avec le taux de plaquettes et la CRP était limitée et inexistante avec la calprotectine fécale).

Si la faible valeur prédictive des biomarqueurs peut résulter de la petite taille de l'échantillon (en particulier, proportion significative de valeurs manquantes en ce qui concerne la calprotectine fécale), cela renforce cependant la notion de capacité de prédiction des signes IRM.

Les quatre signes décrits plus haut peuvent donc être considérés comme prédictifs d'un délai de récidive plus court (médiane) chez les patients cliniquement quiescents.

Cela reste à valider par une étude sur une population plus importante et à mettre en perspective avec l'impact d'éventuelles modifications thérapeutiques ciblées sur la diminution du risque de récidive et de progression de la maladie.

En conclusion, l'inflammation et le dommage tissulaire sont deux éléments qui évoluent de façon différente et pas systématiquement convergente. Même si c'est l'inflammation qui conduit au dommage tissulaire, ils peuvent être complètement dissociés à un moment donné de l'histoire du malade. On peut ainsi retrouver des malades avec une inflammation complètement contrôlée mais souffrant des dommages tissulaires accumulés antérieurement (résections intestinales, sténoses, etc…). A l'inverse, on pourra trouver des malades avec une inflammation importante mais n'ayant pas encore développé de dommages tissulaires. Ce sont ces derniers patients qui répondront le mieux aux traitements médicaux et chez lesquels une rémission profonde et une disparition complète des symptômes sont les plus susceptibles d'être obtenues.

L'IRM, déjà corrélée à l'activité de la maladie, se révèle capable d'évaluer et de quantifier le dommage tissulaire.

Dans ce sens, elle devient incontournable pour l'évaluation de l'impact de la maladie et de ses traitements au long terme.

En outre, elle se révèle potentiellement capable de déterminer l'état de cicatrisation tissulaire à obtenir pour permettre une absence de progression de la maladie.

Puisque c'est le stade de gravité de lésions focales qui influence la récidive plutôt qu'un score global, l'IRM prend tout son intérêt de pouvoir suivre quelques éléments précis et non discutables car évaluables de façon répétitive et fiable.

Les paramètres sémiologiques IRM identifiés sont aisément accessibles à quiconque pratique l'imagerie et sur n'importe quel appareillage technique de mesure.

Cela ouvre la possibilité de réaliser facilement des études multicentriques afin de vérifier ces affirmations sur des populations plus importantes et en pratique clinique de routine.

On pourrait même imaginer qu'un travail de même type soit réalisé pour et/ou en corrélation avec l'endoscopie.

Au-delà de cela, ces résultats impliquent une remise en question des stratégies thérapeutiques que l'ecMR peut évaluer de façon fiable et complète (exploration de tout le tractus

digestif en une procédure), proposant ainsi un monitoring non irradiant de patients le plus souvent jeunes, et dont l'histoire naturelle laisse supposer de multiples recours ultérieurs aux contrôles, notamment par l'image.

Enfin, si le monitoring de la stratégie thérapeutique par ecMR s'avère prometteur dans l'idée de traiter plus rapidement et plus activement des patients qui restent à risque de récidive malgré une relative quiescence clinique et biologique, on peut aussi imaginer que d'autres patients, présentant des signes d'atteinte pariétale persistante à l'ecMR, ne soient pas traités parce que ces signes ne sont pas considérés comme significatifs et qu'ils ne présentent que peu ou pas de risques de rechute en regard du risque délétère potentiel d'un traitement parfois lourd et, en tous cas, jamais anodin.

Gardant à l'esprit l'un des principes fondamentaux de la médecine : « Primum non nocere », ces éléments contribuent à notre progrès vers une médecine plus personnalisée, adaptée aux besoins de chaque patient.

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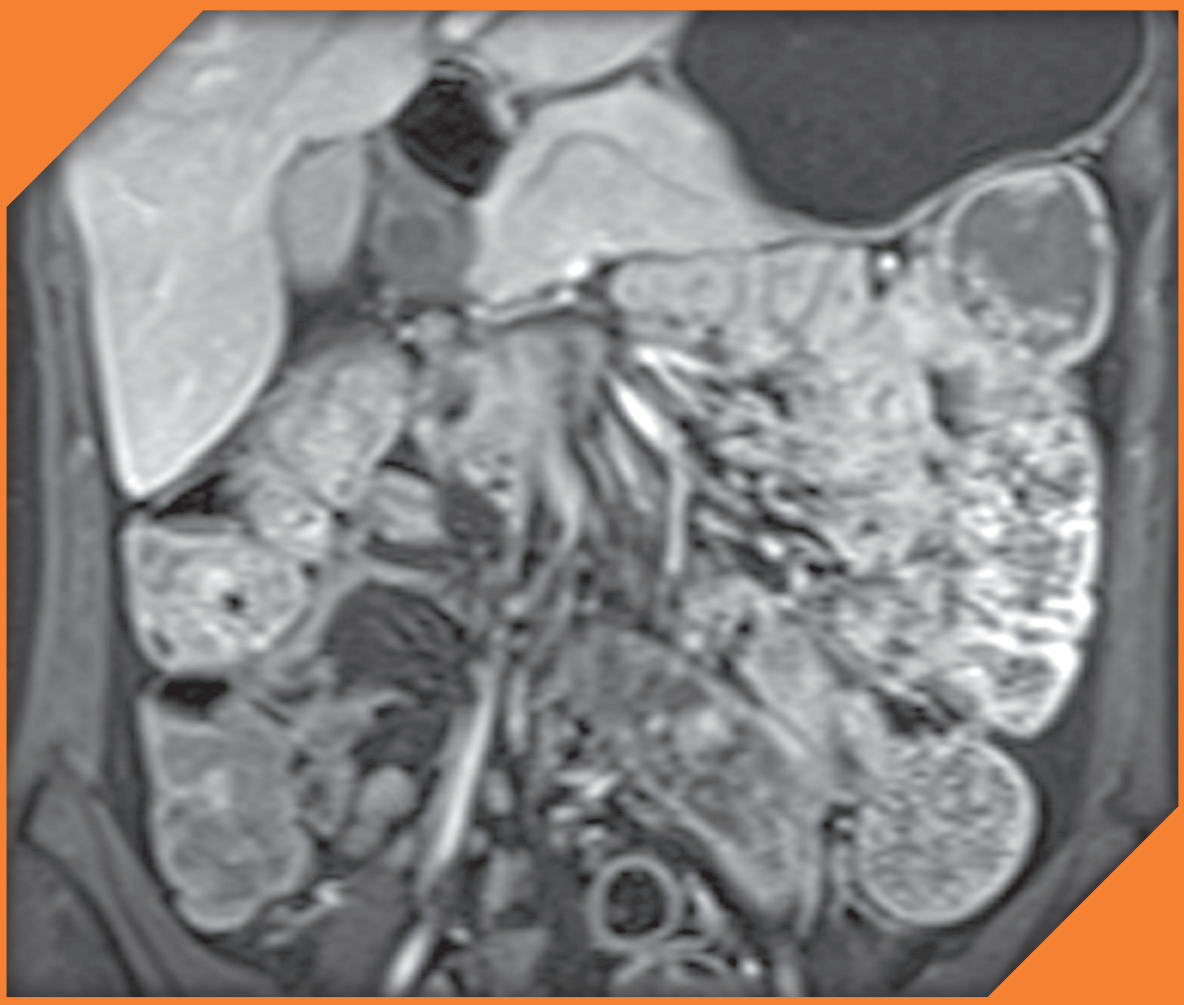

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