The small bowel capsule and management of patients with inflammatory bowel disease

Arnaud Bourreille
Institut des maladies de l'appareil digestif (Imad),
CHU Hôtel Dieu,
Nantes, France

" The management of inflammatory bowel disease (IBD) has changed considerably in recent years with the widespread use of anti-TNF-α antibodies. These treatments have clearly demonstrated their efficacy for the treatment of Crohn's disease (CD) and ulcerative colitis (UC). Unlike previously used molecules – corticosteroids, azathioprine, methotrexate, and 5-aminosalicylates – , anti-TNF-α drugs have the ability to induce healing of endoscopic mucosal lesions in a large number of patients. With their use we have rediscovered the importance of endoscopically visible lesions of the intestinal wall; new management strategies have been developed taking into account these lesions and their evolution with time. In parallel, the renewed interest in morphological exploration of the digestive tract has provided an opportunity to develop noninvasive tools that allow repeated examinations in patients with IBD, and which are effective and acceptable to patients. These modern strategies of management include capsule endoscopy of the small bowel (SBCE), which allows accurate and noninvasive analysis of the gastrointestinal mucosa. This is the only tool that allows a global vision of the lining of the small intestine, which was hitherto impossible because of the lack of a simple tool adapted to this exploration."

The natural history and evolution over time of inflammatory bowel disease

It has been customary to describe inflammatory bowel disease (IBD) as a chronic disease that progresses in successive bursts, interspersed with remission periods of variable length. This description takes into account only the tip of the iceberg, namely clinical symptomatology, and ignores subclinical changes in gastrointestinal inflammation characterized by the presence of persistent intestinal mucosal injury. IBD, especially Crohn's disease (CD), are progressive and destructive diseases; the clinical evaluation of their severity at a given time does not reflect the accumulation of destructive lesions in the intestine. The gradual emergence of stenotic and fistulizing complications, corresponding to subclinical destruction of the gut, has been described in two independent studies performed in reference centers [1, 2]. Patients with a luminal inflammatory disease at the time of diagnosis progressively developed stenotic and/or fistulizing disease. This evolution was also observed in a cohort from the general population, which better reflects the diversity of CD phenotypes outside of reference centers [3].

All anti-TNF-α drugs have the capacity to induce a deep remission, with the disappearance of symptoms and mucosal healing [4-6]. It has been clearly demonstrated in these studies that the percentage of patients with mucosal healing is even greater when the disease is of recent onset. This observation is consistent with the irreversible nature of old lesions, both of inflammatory and scarring origin, for which no treatment can reverse these effects.

The changes in therapeutic goals for IBD originate from the beneficial influence of mucosal healing on the natural history of the disease. In the short and medium terms, it has been demonstrated that the frequency of hospitalization and the need for surgery are significantly reduced when mucosal healing is achieved, in comparison with their frequencies in patients with progressive lesions [7-10]. Conversely, the proportion of patients in remission without corticosteroid treatment, or with neither corticosteroid nor anti-TNF treatment, was higher 2 years after having achieved mucosal healing than in those patients with persistent mucosal lesions [11]. Overall, these data have driven new strategies based on an earlier and more effective treatment of patients with IBD, on obtaining mucosal healing and the disappearance of lesions that are at risk of complications, and finally on an objective mo-

nitoring of the efficacy of the treatments. This monitoring takes into account biological, radiological, and endoscopic data, in which the use of capsule endoscopy will increasingly have a place.

Role of the capsule in the diagnosis of Crohn's disease

Small bowel capsule endoscopy (SBCE) is the examination with the highest diagnostic yield for exploration of the small intestine. Indeed, the meta-analysis of Triester *et al.* [12], updated in 2010 [13], demonstrated the superiority of the capsule in terms of diagnostic yield compared with small bowel transit time: 52% *versus* 16% ($P < 0.0001$); scanner with enterography: 68% *versus* 21% ($P < 0.00001$); and ileocolonoscopy: 47% *versus* 25% ($P = 0.009$) (*table 1*).

A 10% gain was obtained as compared with magnetic resonance imaging enterography (55% *versus* 45%, $P = 0.43$) [13]. It is clear that the SBCE allows the visualization of superficial mucosal lesions that are not visible on conventional radiology, resulting in an increase in diagnostic yield and a better guidance of the diagnostic enteroscopy (oral or rectal route) if this is necessary, in particular to obtain histological samples. The positive and negative predictive values of SBCE were assessed in a recent study [14]. Seventy-five patients suspected of having CD, in spite of a normal colonoscopy and a normal radiological examination of the small bowel, were included in this study. All patients underwent SBCE and were then followed up for an average of 13 months. The positive and negative predictive values of the SBCE for the diagnosis of CD were 87% and 96%, respectively [14].

In light of these results, the joint recommendations of ECCO (the European Crohn's and Colitis Organization) and the World Organization of Digestive Endoscopy (OMED), published in 2009 [15], were amended in 2013 [16]. While in 2009 it was recommended to perform a radiological examination of the small bowel before performing an SBCE, experts now recommend carrying out an examination of the small bowel by capsule endoscopy or by radiology when conventional endoscopy does not permit a diagnosis of CD [16]. Considering its negative predictive value, it is unnecessary to perform further tests if the SBCE is normal.

Table 1. Additional diagnostic yield of the capsule compared with conventional techniques for exploration of the small intestine, from [13].

		Studies (n)	Patients (n)	Additional diagnostic yield (CI) 95 %)
Capsule *vs* enteroscopy	Suspicion of CD	2	46	0.18 (-0.23 – 0.59)
	Known CD	2	56	0.57 (0.43 – 0.71)
Capsule *vs* small bowel transit time	Suspicion of CD	8	155	0.32 (0.16 – 0.48)
	Known CD	10	224	0.38 (0.22 – 0.54)
Capsule *vs* . CT enterography	Suspicion of CD	3	53	0.47 (0.31 – 0.63)
	Known CD	3	66	0.47 (0.31 – 0.63)
Capsule *vs* MRI enterography	Suspicion of CD	3	31	0.10 (-0.14 – 0.34)
	Known CD	4	63	-0.06 (-0.30 – 0.19)

CD: Crohn's disease; MRI: magnetic resonance imaging; CT : computed tomography.

Monitoring of Crohn's disease patients

In the case of known CD, it has also been clearly demonstrated that SBCE has a better performance compared with conventional diagnostic tests. The SBCE is better:

- than enteroscopy: 66% *versus* 9% ($P < 0.00001$) (*table 1*);
- than small bowel transit time : 71% *versus* 36% ($P < 0.00001$);
- than computed tomodensitometry enterography (CTE): 71% *versus* 39% ($P < 0.0001$);
- than MRI with enterography or enteroclysis [13].

Only SBCE allows the detection of early superficial mucosal lesions

that are undetectable by radiological techniques. SBCE is also able to detect lesions of the proximal small bowel, which is not possible with MRI or CT examinations with enteroclysis or enterography [17,18]. In a first study, the sensitivity and specificity of SBCE to diagnose an ileal involvement were 100% and 91%, respectively, while those of MRI were 81% and 86%, and those of CT, 76% and 85%. The other improvement was the detection of proximal lesions in 18 patients, as opposed to 2 patients and 6 patients for MRI and CT, respectively [17]. Similar results were published in a second study that compared MRI and SBCE [18]. The importance of the proximal small bowel mucosal lesions detected by SBCE was recently suggested in a cohort study [19]. In this study, 108 patients with CD had a median follow-up of 24 months (IQ: 8-46) after the completion of a capsule endoscopic examination of the small bowel, and 50% had a relapse during follow-up. The only independent risk factor for relapse was the presence of endoscopic lesions in the proximal small bowel, with a hazard ratio of 1.99 (95% CI, 1.10–3.21). These results highlight the potential value of detecting proximal small bowel lesions to optimize the treatment of patients with CD. Studies evaluating surveillance, with and without capsule endoscopy, of the evolution of the disease, the frequency of complications, of bowel resections, and of hospitalizations, are nevertheless lacking. Some data are available regarding the possibility of observing changes in endoscopic lesions visualized using the capsule, notably following anti-TNF therapy. These preliminary data represent an essential first step before assessing a surveillance of the patients with the capsule [20,21]. In this latter study, there was no correlation between the changes in endoscopic severity score in the small bowel (Lewis score) and the changes in clinical activity and quality of life scores [21]. The authors proposed that endoscopic data be considered as independent surveillance and evaluation criteria. It is also possible that the severity index used in the overall evaluation of the small bowel may not be suitable for the assessment of changes induced by treatments. These facts highlight the importance of defining precisely the evolutive potential of each of the lesions visible with the capsule, and probably of considering differently aphthous erosions and superficial or deep ulcerations. For now, we can only extrapolate the data demonstrating the importance of endoscopic healing observed in colonoscopy and imagine that this will be the same for the capsule
.

Risk of impaction of the capsule in Crohn's disease

One of the limitations to the use of the capsule is the risk of impaction in the event of stenosis of the small bowel. Surgery or endoscopic dilatation may then be necessary to recover the video capsule. The risk of impaction is significantly increased in patients with known CD [22]. In 2009 [15] it was recommended that examination of the small bowel by CT or MRI be performed to rule out stenosis. These recommendations did not take into account the possibility of eliminating the risk of impaction by first ingesting a "dummy" capsule, the Patency Agile ®, whose main feature is its ability to dissolve within a determined time frame. Initial studies tested two generations of Patency Agile ®, with different dissolution times, which explains the conflicting results obtained: in any case these results were insufficient to eliminate the risk of impaction of the video capsule during a stenosis of the small bowel. The latest-generation Patency Agile ® starts to dissolve from the 30th hour after ingestion. Its passage intact within the allotted time, or disappearance on a radiological examination of the abdomen, can almost completely eliminate the risk of impaction, with a yield at least equal, if not superior, to that of conventionally used radiological examinations [23]. In the updated recommendations [16], the Patency Agile ® can be used equivalently to conventional radiological examinations to minimize the risk of capsule impaction. Moreover, if new patient management strategies and the early initiation of effective treatments to heal the mucosa are applied, the risk of digestive stenosis should steadily decrease and eventually disappear. This strategy would give a clear role to capsule endoscopy in the monitoring of patients.

Conclusion

In parallel with the provision of effective new molecules for the treatment of IBD, therapeutic goals will change until macroscopic and even histological healing of the digestive mucosa is achieved. The necessary monitoring of the patients to ensure that these goals are attained requires the development of minimally or non invasive tools allowing repeated follow-up of patients. Capsule endoscopy, given its characteristics and performance, would seem ideally suited to management strategies for patients with IBD, not only in the initial diagnosis but also for patient monitoring, as illustrated in *figure 1*.

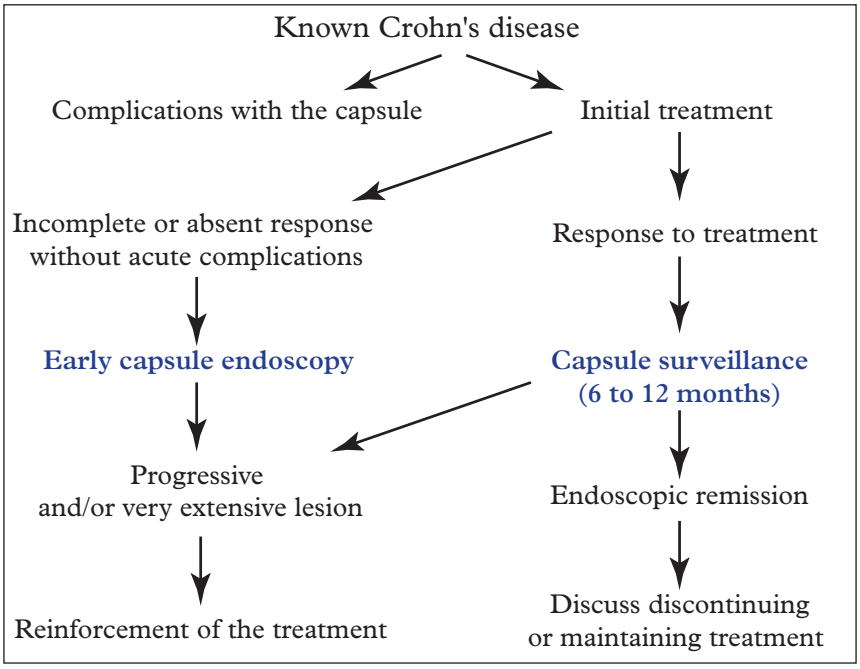

Figure 1. Algorithm for Crohn's disease.

Conflicts of interest

Arnaud Bourreille has links as an expert or as a speaker with the following companies: Abbvie, Ferring, Given Imaging, MSD, Norgine, and Takeda.

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