Digestive and Liver Disease 49 (2017) 457–458

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Commentary

Beyond remission and mucosal healing in Crohn's disease. Exploring the deep with cross sectional imaging

Giovanni Maconi*, Alessandro Armuzzi

Gastroenterology Unit, Department of Biomedical and Clinical Sciences, L. Sacco University Hospital, Milan, ItalyIBD Unit, Presidio Columbus, Fondazione Policlinico Gemelli Università Cattolica, Rome, Italy

The targets of therapy in inflammatory bowel disease (IBD) have changed in recent years. A growing body of evidence has shown that biologics allow treating beyond the symptoms, making healing of the mucosa of the damaged bowel the new goal of therapy [1]. Endoscopic mucosal healing (MH) is associated with a stable steroid-free remission, a longer time to relapse after drug withdrawal and a lower rate of hospitalizations and surgery [1,2].

Crohn's disease (CD), unlike ulcerative colitis (UC) that affects the mucosal surface, is characterised by transmural inflammation. Therefore, whether MH in CD reflects the complete healing of the damaged bowel wall, is uncertain and still matter of debate. Hence, a new concept of deep healing, involving the whole intestinal wall in CD, the transmural healing (TH), has been developed. This is the normalization of the thickening of the bowel walls, assessed by cross sectional imaging, which should reflect the complete resolution of the bowel damage. The TH has been considered as an end point parameter by few studies, so far [3–10].

Cross-sectional diagnostic imaging scores, mainly based on using magnetic resonance enterography (MRE) and intestinal ultrasound (IUS), have been developed to evaluate and quantify bowel damage and intestinal complications in CD [11]. This with the aim to monitor its progression during disease course [12] or to assess its improvement and resolution after treatment [6,13]. Various MRE indices have been developed for assessing CD activity.The most reliable, the MaRIA score, relies on the sum of various parameters such as wall thickening, contrast enhancement, oedema and ulceration for each of bowel wall segment [14]. This validated and reproducible score, is able to accurately assess endoscopic activity and provide criteria of TH that correlate with MH. Although valid in clinical practice, this score is mainly useful in clinical studies to monitor biologic treatment in CD [13,15]. In clinical practice, the simple normalization of bowel wall thickening, without signs of hypervascularization, is usually adopted as criteria for TH in CD [3].

A sonographic quantitative index (the sonographic lesion index for CD [SLIC]) has been also developed by using the small intestine contrast ultrasound (SICUS) to quantify CD anatomical damage of the small bowel and to monitor its behaviour under therapy [6]. However, to date, reproducible sonographic scores, validated by comparing IUS findings with endoscopic ones (e.g., CDEIS or SES-CD), are still lacking. Most studies have correlated IUS findings, namely the TH defined as the simple normalisation of bowel wall thickening (< 3 mm), with endoscopic MH [3,4,7].

Thanks to their non-invasiveness and high accuracy, MRE and IUS are considered the most useful cross-sectional diagnostic procedures for assessing CD, and the most appropriate to monitor CD patients after treatment. Systematic reviews, meta-analyses, and prospective comparative studies, have shown that both have high accuracy to detect CD and its intestinal complications [16]. However, data regarding their usefulness in the follow up of CD are still scarce.

In this issue, the observational study by Castiglione et al. has prospectively followed 40 CD patients, under treatment with biologics. The authors have assessed the two-year steroid-free clinical remission, MH and TH by means of IUS and MRE [3]. The study shows that TH was achieved in approximately a quarter of patients, and in all patients this was associated with clinical remission. Conversely, only less than half of patients in clinical remission and a proportion of those with MH, had also a TH. The study also showed that TH was more frequent in patients with lower pre-treatment endoscopic activity (assessed by the SES-CD score) and short duration of CD (<2 years). Noteworthy, the high agreement between TH assessed by IUS and that detected by MRE (k = 0.9), with only 1 false positive healing by IUS.

The findings of this study are in keeping with the few data of the literature showing that parietal healing in CD is reached in no more than 14% of patients at 1 year [2] and in less than 30% of patients after 2 years of biologic treatment [3,7,8], and that, as expected, it is harder to achieve than MH. Therefore, TH likely reflects a more deep level of healing, which could be correlated with a more stable and long lasting clinical remission. This also concurs with what we know about the histological and biochemical remission in UC. It has been observed that microscopic inflammation persists in 16–100% of patients with endoscopically quiescent disease

* Corresponding author.
E-mail addresses: giovanni.maconi@unimi.it (G. Maconi), alearmuzzi@yahoo.com (A. Armuzzi).

http://dx.doi.org/10.1016/j.dld.2017.04.009

[17–19] and that this is predictive of clinical relapse in the following 12 months of follow-up [18]. Likewise, high levels of faecal calprotectin in patients with deep remission are well recognized as a relevant predictive factor for both endoscopic and clinical relapse [19,20]. However, the prognostic role of cross sectional assessment of TH, faecal calprotectin and microscopic inflammation, alone or in combination, remains to be fully investigated in CD. This aspect is a relevant issue in order to assess the depth of remission, and to discriminate which patients can stop or have to continue the treatment, despite deep remission.

On the other hand, Castiglione's study confirms that also clinical factors are predictive of response. In particular, the less severe pretreatment endoscopic activity and short CD duration seem to be associated with a higher prevalence of remission and also a greater prevalence of TH. This observation likely means that biologic treatment may have a more favourable effect on disease damage in earlier phases of CD, when chronic consequences of inflammation and likely fibrosis have not yet taken place. On this regard, preliminary studies have shown that the early reduction of vascularity (at 1 month), assessed by means I.V. contrast enhanced IUS, could predict the therapeutic response to biologics [21–23], but stability of this result in the long term remains to be demonstrated.

The last aspect pointed out by the study is the comparable diagnostic performance of IUS and MRE. This is not surprising, as several studies have shown the comparable accuracy of these technique in detecting CD and assessing its complications [11]. However, the study by Castiglione et al. showed for the first time also their equivalent accuracy in monitoring the disease after biologic treatment, by providing useful information for patients' management.

In the choice of the technique, several factors should be taken into account. MRE has some advantages over IUS, as it provides a wider panoramic view, it allows the detection and follow up of lesions located in sites more difficult to assess by IUS like jejunum and rectum, and it offers the opportunity to be reassessed off-line. Conversely IUS is potentially more widely available (providing that sonographers with adequate skill and experience are available), is quick and ready to use, easily repeatable, and cheaper than MRE. In particular, the latter are relevant issues in patients who need numerous follow up visits and close monitoring of treatment.

Irrespective of the method used to assess TH (which usually depends more on local availability than on other issues), Castiglione et al.'s study confirms that IUS and MRE are valuable tools for CD monitoring, not only to early evaluate disease complications but also to assess the degree of deep remission.

Moreover, we believe that these technique are not in competition or necessarily alternative in the management of CD patients. Their combination might be also advisable, in clinical practice, in particular at the start of the follow up. The use of both techniques can provide a more accurate and definite description of complex conditions and, providing that IUS is able to give the same information as MRE, the former can be used to monitor the disease, saving costs and time.

References

[1] Armuzzi A, Van Assche G, Reinisch W, Pineton de Chambrun G, Griffiths A, Sladek M, et al. Results of the 2nd scientific workshop of the ECCO (IV): therapeutic strategies to enhance intestinal healing in inflammatory bowel disease. Journal Crohns Colitis 2012;6:492–502.

[2] Peyrin-Biroulet L, Ferrante M, Magro F, Campbell S, Franchimont D, Fidder H, et al. Results from the 2nd Scientific Workshop of the ECCO. I: impact of mucosal healing on the course of inflammatory bowel disease. Journal Crohns Colitis 2011;5:477–83.

[3] Castiglione F, Mainenti P, Testa A, Imperatore N, De Palma GD, Maurea S, et al. Cross-sectional evaluation of transmural healing in patients with Crohn's disease on maintenance treatment with anti-TNF alpha agents. Digestive and Liver Disease 2017. Feb 28. pii: S1590-8658(17)30238-4.

[4] Civitelli F, Nuti F, Oliva S, Messina L, La Torre G, Viola F, et al. Looking beyond mucosal healing: effect of biologic therapy on transmural healing in Pediatric Crohn's Disease. Inflammatory Bowel Diseases 2016;22(October (10)):2418–24.

[5] Eder P, Katulska K, Krela-Kaźmierczak I, Stawczyk-Eder K, Klimczak K, Szymczak A, et al. The influence of anti-TNF therapy on the magnetic resonance enterographic parameters of Crohn's disease activity. Abdominal Imaging 2015;40:2210–8.

[6] Zorzi F, Stasi E, Bevivino G, Scarozza P, Biancone L, Zuzzi S, et al. A sonographic lesion index for Crohn's disease helps monitor changes in transmural bowel damage during therapy. Clinical Gastroenterology and Hepatology 2014;12:2071–7.

[7] Castiglione F, Testa A, Rea M, De Palma GD, Diaferia M, Musto D, et al. Transmural healing evaluated by bowel sonography in patients with Crohn's disease on maintenance treatment with biologics. Inflammatory Bowel Diseases 2013;19:1928–34.

[8] Tielbeek JA, Löwenberg M, Bipat S, Horsthuis K, Ponsioen CY, D'Haens GR, et al. Serial magnetic resonance imaging for monitoring medical therapy effects in Crohn's disease. Inflammatory Bowel Diseases 2013;19:1943–50.

[9] Grover Z, Muir R, Lewindon P. Exclusive enteral nutrition induces early clinical, mucosal and transmural remission in paediatric Crohn's disease. Journal of Gastroenterology 2014;49:638–45.

[10] Van Assche G, Herrmann KA, Louis E, Everett SM, Colombel JF, Rahier JF, et al. Effects of infliximab therapy on transmural lesions as assessed by magnetic resonance enteroclysis in patients with ileal Crohn's disease. Journal of Crohns and Colitis 2013;7:950–7.

[11] Magarotto A, Orlando S, Coletta M, Conte D, Fraquelli M, Caprioli F. Evolving roles of cross-sectional imaging in Crohn's disease. Digestive and Liver Disease 2016;48:975–83.

[12] Amitai MM, Zarchin M, Lahat A, Yablecovitch D, Neuman S, Levhar N, et al. Israeli IBD. research Nucleus (IIRN). Structural bowel damage in quiescent Crohn's disease. Digestive and Liver Disease 2017. Feb 13. pii: S1590-8658(17)30201-3. 10.1016/j.dld.2017.02.001. [Epub ahead of print].

[13] Ordás I, Rimola J, Rodríguez S, Paredes JM, Martínez-Pérez MJ, et al. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. Gastroenterology 2014;146, 374-82.e.

[14] Rimola J, Alvarez-Cofiño A, Pérez-Jeldres T, Ayuso C, Alfaro I, Rodríguez S, et al. Comparison of three magnetic resonance enterography indices for grading activity in Crohn's disease. Journal of Gastroenterology 2016 [Epub ahead of print].

[15] Stoppino LP, Della Valle N, Rizzi S, Cleopazzo E, Centola A, Iamele D, et al. Magnetic resonance enterography changes after antibody to tumor necrosis factor (anti-TNF) alpha therapy in Crohn's disease: correlation with SES-CD and clinical-biological markers. BMC Medical Imaging 2016;16:37.

[16] Panes J, Bouhnik Y, Reinisch W, Stoker J, Taylor SA, Baumgart DC, et al. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. Journal of Crohns and Colitis 2013;7:556–85.

[17] Bryant RV, Winer S, Travis SPL, Riddell RH. Systematic review: histological remission in inflammatory bowel disease: Is complete remission the new treatment paradigm? An IOIBD initiative. Journal of Crohns and Colitis 2014;8:1582–97.

[18] Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean. Gut 1991;32:174–8.

[19] Gisbert JP, Marín AC, Chaparro M. Systematic review: factors associated with relapse of inflammatory bowel disease after discontinuation of anti-TNF therapy. Alimentary Pharmacology and Therapeutics 2015;42:391–405.

[20] Mooiweer E, Severs M, Schipper ME, Fidder HH, Siersema PD, Laheij RJ, et al. Low fecal calprotectin predicts sustained clinical remission in inflammatory bowel disease patients: a plea for deep remission. Journal of Crohns and Colitis 2015;9:50–5.

[21] Ripollés T, Paredes JM, Martínez-Pérez MJ, Rimola J, Jauregui-Amezaga A, Bouzas R, et al. Ultrasonographic changes at 12 weeks of anti-tnf drugs predict 1-year sonographic response and clinical outcome in Crohn's disease: a multicenter study. Inflammatory Bowel Diseases 2016;22:2465–73.

[22] Saevik F, Nylund K, Hausken T, Ødegaard S, Gilja OH. Bowel perfusion measured with dynamic contrast-enhanced ultrasound predicts treatment outcome in patients with Crohn's disease. Inflammatory Bowel Diseases 2014;20:2029–36.

[23] Quaia E, Sozzi M, Angileri R, Gennari AG, Cova MA. Time-intensity curves obtained after microbubble injection can be used to differentiate responders from nonresponders among patients with clinically active Crohn disease after 6 weeks of pharmacologic treatment. Radiology 2016;281:606–16.