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REVIEW ARTICLE

'Treat to Target' in Mild to Moderate Ulcerative Colitis: Evidence to Support this Strategy

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Abstract: ***Background*:** The management of chronic conditions, above all rheumatic disease and diabetes, now incorporates a "treat to target" strategy where treatment aims to achieve objective outcomes; this has emerged to be applicable in ulcerative colitis (UC) as well. Targets are demonstrated to prevent end-organ dysfunction, specifically bowel damage and its complications, and lastly colorectal cancer. Recently, the scientific community has tried to define further targets beyond those currently recommended, namely mucosal healing and clinical remission. Studies that prospectively investigated this approach in UC are scanty and a treat-to-target (T2T) algorithm is not routinely used in daily clinical practice.

***Objective*:** We aim to review current evidence on T2T in UC and discuss its adoption in routine clinical practice as well as in clinical trials.

***Methods*:** A PubMed search was conducted in February 2020 to identify published papers investigating targets' achievement rates in UC.

***Results*:** Different targets can be achieved through approved drugs for mild to moderate UC; histological remission is emerging as a robust target with respect to long-term outcomes.

Conclusion: Further studies to compare a T2T strategy with the traditional care are needed, particularly in the mild to moderate spectrum of disease.

Keywords: Ulcerative colitis, histological healing, mucosal healing, inflammation, target, remission.

1. INTRODUCTION

In the very last years, much effort has been made by the scientific community to identify therapeutic targets that could modify the natural history of ulcerative colitis (UC). The chronic and potentially progressive feature of the disease necessarily imply for clinicians to consider colectomy, dysplasia or cancer occurrence, hospitalization rates as well as progression in extension and relapse rate as the main challenges in the clinical management of UC [1].

The first evidence-based experience on a treat-to-target (T2T) strategy in patients with inflammatory bowel disease (IBD) came from Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE). "The primary goal of treating patients with IBD is to maximize the long-term health-related quality of life through control of symptoms, prevention of structural damage, normalization of function and participation in social and work-related activities" as stated by the STRIDE. The proposed outcome is a composite clinical remission expressed as patient-reported outcomes (PROs) (defined as resolution of rectal bleeding and diarrhea) together with endoscopic remission (defined as a Mayo endoscopic score of 0-1) [2].

It is well established that mere clinical endpoints have limitations: 25% of patients who are clinically asymptomatic have endoscopically active disease (Mayo score > 1); nevertheless, in the presence of endoscopic and even histological remission, symptoms continue to be reported (10% for rectal bleeding and 27% for diarrhea) [3-5]. Moreover, histological inactivity did not influence the rate of patients reporting symptoms compared to endoscopic remission alone [6].

The CALM study, an open-label, randomized, controlled phase 3 study, demonstrated that close monitoring of biomarkers is a powerful tool to drive clinical decisions and improve clinical and endoscopic outcomes in patients with IBD [7].

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So far, mucosal healing (MH) is the recommended therapeutic goal [8], confirmed by metanalysis to be associated with long-term clinical remission, avoidance of colectomy, and corticosteroid-free clinical remission [9]. MH in UC corresponds to the absence of friability, blood, erosions and ulcers in all visualized segments of the colonic mucosa and identifies Mayo sub-score 0 -1 [8], with a slightly worse disease course for Mayo 1 [2].

There is intense debate on whether histological healing (HH) might overcome MH as an ultimate goal in UC and whether MH should be re-defined with the involvement of HH. According to STRIDE consensus, HH was rather considered as an adjunctive goal, not incorporated in recommendations due to limited standardization and validation [2]. Still, the achievement of MH remains unsatisfactory since sustained clinical remission, long-term colectomy rates, hospitalization, and dysplasia and/or cancer occurrence have not significantly decreased over the last years [10].

The cumulative risk of colon-cancer in UC patients increases with disease duration (2% at 10 years, 8% at 20 years, *etc*.), disease extent, and concomitant primary sclerosing cholangitis [11]; generally, in UC the risk of colorectal cancer (CRC) is 2.4 - fold compared with the general population [11].

Recently, *Danese et al.*, introduced the concept of "disease clearance" as a combination of symptomatic remission and MH, integrating HH to endoscopic healing and proposed this achievement as the ultimate target in UC [12].

In many fields of medicine, especially in the management of chronic conditions, a "treat to target" strategy has been proposed where treatment outcomes are defined by objective and measurable endpoints. The strategy finds its basis in the failure of traditional outcomes in detecting a sub-clinical smoldering disease that leads to damage over time [13, 14]. In this approach, therapy is modified or optimized until the specific target is achieved, with the aim of reducing end-organ dysfunction, specifically the bowel affected by UC.

Moreover, a T2T strategy in UC would eventually mean a "multi-target" approach, including clinical remission, endoscopic MH, HH, imaging, biomarkers and in the distant future, even molecular remission assessments [15-17].

Although in the biologics era, the greatest attention has been given to the management of moderate to severe UC, most of the patients diagnosed with UC experience a mild to moderate disease course that remains at low risk of colectomy. According to Montreal classification, mild to moderate UC presents with a rather low number of daily stools (≤ 4) and the absence or exiguous presence of systemic signs of inflammation (*i.e*. fever and tachycardia) [18]. Beyond gastroenterologists, primary care physicians frequently manage these patients and clinical practice may considerably vary.

Our aim was to review the current evidence on T2T algorithm analyzing the different therapies available for mild to moderate UC and to discuss limitations and advantages of adopting it in the every-day clinical practice.

2. THERAPIES AND OUTCOMES

Data about outcomes with the different therapeutic targets, divided into clinical remission, endoscopic and histological healing, are reported below for any drug-class approved for the treatment of UC.

2.1. Mesalamine (5-ASA) and Azathioprine

5-aminosalicylate (5-ASA) compounds, oral, topical or in combination, depending on disease distribution and severity, are the first-choice treatment for induction and maintenance of active, mild to moderate UC. In population-based cohorts, it has been estimated that more than 90% of UC patients receive 5-ASA within 1 year from diagnosis and, in the long-term, around two-thirds of the patients continue the therapy with 5-ASA [19].

Treatment with standard-dose (2-3 g/day) and high-dose (> 3g/day) of 5-ASA is able to achieve different targets in UC patients. Table (**1**) summarizes the data on mesalamine. Starting from clinical remission, 5-ASA induces combined clinical and endoscopic remission after 8 weeks of treatment in about 37% of UC patients [20]; remission occurs regardless of disease extent or severity and previous exposure to low dose 5-ASA [21]. As maintenance treatment, clinical remission rates for mesalamine were assessed to be around 60% [22]. The high safety profile of 5-ASA compounds is a strength of this therapy and, importantly, the different mesalamine formulations are comparable in terms of efficacy and safety [23].

With respect to MH, oral and rectal 5-ASA in combination is known to induce MH in about 69% of patients affected by active mild to moderate UC [24].

Concerning HH as a target, the administration route (*i.e*. oral *vs* rectal) influences remission rates [25]: combination therapy is more effective compared with oral or topical 5-ASA alone, with reported efficacy reaching up to 80% in achieving MH [25, 26].

Data on MH from a recent meta-analysis on randomized controlled trials in mild to moderate UC, including patients on oral or rectal therapy, show that 5-ASA compounds induce MH, globally, in approximately 50% of patients, without any significant difference between the distinct 5-ASA agents available [27]. Precisely, 5-ASA rectal suspensions and suppositories succeeded in 51% and 46% for foam and enema each, while the proportion of MH was 62% for suppositories: with concomitant histologic remission in 37.2% and 44.9%, respectively [27]. HH was observed in 30.1% of the patients on oral 5-ASA [27].

The phase 3b/4, open-label, multi-center study (MOMENTUM trial) that investigated the efficacy of 5-ASA in maintenance in mild to moderate UC in remission after induction with multimatrix mesalamine 4.8 g/day (for 8 weeks), reported the achievement of an endoscopic modified UC-DAI score ≤ 1 at 12-months in 76.4% (139/182) of the patients who had complete remission after induction [28]. 5-ASA is efficient in inducing histological improvement (defined as a reduction in Nancy score). *Bajpai et al.*, demonstrated histological improvement rate in 59.7% of patients in their observational study on serial colon biopsy specimens of mild to moderate UC patients on long-term 5-ASA therapy [29].

Lasson et al., proposed a fecal calprotectin (FC) target value of >300 ug/g to optimize treatment before symptomatic

Table 1. Achievable targets in mild to moderate UC treated with 5-ASA and azathioprine.

Reference	Investigated Target	Study Design	Intervention	Results
Lichtenstein *et al.* [20]	Clinical remission, MH	Randomized, controlled	MMX mesalamine 2.4 g/day twice daily for 8 weeks	37.5% and 34.1% of the patients (*n*=88) achieved clinical remission and combined clinical + endoscopic remission, respectively
Lichtenstein *et al.* [21]	Clinical remission, MH	Randomized, controlled	MMX mesalamine 2.4 g/day or 4.8 g/day for 8 weeks	Combined clinical and endoscopic remission occur irrespective of disease extension/severity and previous exposure to low dose 5-ASA
Meucci *et al.* [24]	Clinical remission, MH	Prospective	5-ASA 4 g/day orally and 2 g/day topical for 6 weeks	75.3% of the patients (*n*=81) achieved clinical remission; 69.1% had concomitant MH (Mayo sub-score ≤ 1)
Römkens *et al.* [27]	MH, HH	Meta-analysis	Oral or topical 5-ASA	With regard to oral 5-ASA, 49% of patients treated with granulate achieved MH and 34,9% with tablets. The MH rate was 62% for suppositories, 51% for foam and 46% for enema, respectively Concomitant HH was observed in 37.2 - 44.9%, for topical administrations and in 30.1% of patients on oral 5-ASA
Rubin *et al.* [28]	Clinical remission, MH	Prospective	MMX 4.8 g/day for 8 weeks, followed by 12 months 2.4 g/day	MH (UC-DAI ≤ 1) at 12-months was present in 76.4% (*n*=182) of patients that had complete remission after induction
Bajpai *et al.* [29]	HH, gene expression	Observational	long-term 5-ASA maintenance	Histological improvement rate was observed in 59.7% of patients; COX-2 and IL-8 transcript levels correlated (P ≤ 0.05) with Nancy histological score
Lasson *et al.* [30]	Clinical relapse	Randomized, controlled	FC > 300mg/g was the cut-off for dose escalation of oral 5-ASA	28.6% (*n*=28) of the patients in the active intervention arm relapsed *vs*. 57.1% in the control group (p<0.05)
Prieux-Klotz *et al.* [31]	MH, HH	Retrospective	2-2.5 mg/kg/day AZA or 1.5 mg/kg/day MPT	MH (defined as Mayo ≤ 1) was observed in 43.7% (n=80) after a mean follow-up of 3 years HH (defined as the absence of ulceration, abscesses and inflammatory infiltrate) was observed in 38% after a mean follow-up of 3 years
Giugliano *et al.* [32]	MH, HH	Prospective, pediatric population	AZA for 52 weeks	Among patients in clinical remission after 1 year of AZA, endoscopic healing was present in 76.9% (*n*=26) No correlation between endoscopic and histologic scores.

UC: ulcerative colitis; 5-ASA: 5-aminosalycilates; MMX: multi matrix system; MH: mucosal healing; HH: histological healing; UC-DAI: UC–Disease Activity Index; FC: fecal calprotectin, AZA: azathioprine; MPT: mercaptopurine.

relapse. In their recent prospective study on patients on maintenance treatment with oral 5-ASA, the authors performed a dose escalation of the 5-ASA preparation in the group of patients randomized to the intervention group (28/51) at a cut-off value of FC >300 ug/g: after 5-ASA dose escalation in 18/28 (64.3%) patients, FC value fell < 200 ug/g [30]. Furthermore, over an 18-month follow-up, no patient relapsed nor started a biologic drug [30]. No further prospective interventional studies, properly designed with a T2T strategy, are available.

The adjustment of therapy based on patient self-monitoring of FC values and clinical symptoms according to PRO 2 scoring *vs*. as *per recommended standard practice* is under investigation, as a primary objective, in the ongoing trial *OPTIMISE* (*clinicaltrials.gov* NCT043340895), a phase 4 interventional trial. In detail, the target considered in the primary endpoint in this latter trial will be the endoscopic MH, defined as Mayo score endoscopic subscore = 0, in mild to moderate UC patients in maintenance therapy with 5-ASA ≤ 2.4 g, at 12 months of follow-up.

No studies about a T2T approach in UC patients treated with azathioprine (AZA) are available and a few studies investigated the achievement of targets such as mucosal or histological healing rates with this therapy. In (Table **1**) mucosal healing and histological healing rates for azathioprine are summarized. In a retrospective study by *Prieux-Klotz et*

al. that included 80 UC patients treated with thiopurines (in detail, 78/80 with AZA) as monotherapy for at least 6 months, after a mean follow-up of 3 years, mucosal healing (defined as Mayo ≤ 1) and histological healing (defined as the absence of ulcerations, abscesses and inflammatory infiltrate) were observed in 43.7% and 38% respectively [31]. A therapy duration longer than 2 years was identified as an independent predictor of mucosal healing [31]. Moreover, in this series, 85.7% of the patients with endoscopic mucosal healing also achieved HH [31].

Concerning prospective data, a recent prospective observational study by *Giugliano et al.*, that assessed histological healing as the primary outcome in children with IBD in clinical remission after 1 year of AZA, showed that AZA induced endoscopic healing in 76.9% of UC children (20/26 patients): notably, no HH was documented [32].

2.2. Biologics

Compared with conventional therapies (5-ASA, AZA) in mild to moderate UC, the T2T strategy with respect to biologic drugs has been more extensively investigated; biologics are, however, approved only for moderate to severe active UC. Response to anti-TNF drugs is not homogeneous: 10 to 30% of primary non-response and 50% of loss of response over time occur in IBD patients, with a consequent need to intensify the dose or discontinue the therapy [17, 33]. Targets' achievement rates on biologic drugs are reported in Table (**2**).

With respect to the clinical target, retrospective data by *Nasuno et al.*, from 125 patients with moderate to severe, steroid-refractory, active UC treated with infliximab (IFX), showed that 56/70 patients in clinical remission had clinical activity index score of ≤ 4 at 6 weeks, and they achieved sustained clinical remission at 1 year; in this cohort, steroid-free remission rate at 1 year was achieved in 43% of the cases [34].

Concerning drug-monitoring, *Papamichael et al.*, in their multicenter retrospective study on patients with moderate-to-severe UC on maintenance therapy with IFX, assessed the association of IFX trough levels with endoscopic and histological remission. Optimal IFX threshold concentration for endoscopic healing was identified as ≥7.5 μg/mL and ≥10.5 μg/mL for HH [35]. In a T2T approach, in patients with subtherapeutic trough levels, drug optimization would be more favorable rather than switching to another anti-TNF agent; oppositely, patients with satisfactory drug levels are suitable for changing to a different class of biological agents [33, 36].

In an observational study by *Naviglio et al.*, on pediatric IBD patients that included 15 moderate-to-severe cases of UC, a cut-off value of IFX concentration of 3.11 ug/ml at week 14 was identified as a predictor of persistent remission at week 54 [37].

Regarding histological remission as a target (defined as Geboes index ≤ 3), *Magro et al.*, in their multi-center trial on moderate to severe active UC treated with IFX, assessed a sustained histological remission at week 52 in about 66% of patients who achieved histological remission at week 8 and in about 83% of patients with HR at week 30 [38]. The authors observed a comparable tendency of clinical remission, FC levels and MH with histology [38]. An Italian multicenter retrospective study, including 118 patients affected by UC treated with IFX and followed up for 42 months reported histological remission at 6-months as a predictor of long-term remission [39]. In this population, clinical remission at 42-months was 70.4% and colectomy occurred in 2.7% over the study period [39]. With respect to biomarkers, low hemoglobin and higher C-reactive protein (CRP) have a predictive role in loss of remission in UC patients treated with IFX [39].

Regarding Adalimumab, with respect to clinical remission as a target, some authors observed a successful steroid tapering in steroid-dependent patients in the long term and, if clinical remission was achieved, the cumulative non-relapse survival rate at 6 years was 43.8%; while colectomy-free survival rate was 85.7% [40]. With regard to histological remission rates on therapy with adalimumab, in a retrospective study on anti-TNF naïve adults with moderate to severe active UC, 26.5% histological remission rate was achieved at week 52 [41]; CRP and FC were correlated both to mucosal healing and histological remission without any statistical difference [41].

In UC patients, adalimumab concentration in serum during maintenance therapy is associated with objective therapeutic outcomes: higher levels are found in patients with biochemical, endoscopic or histological remission than in patients without remission; adalimumab concentration threshold with statistical significance in terms of sensitivity and specificity in predicting biochemical response was identified to be 10.5 μg/ml and 16.2 μg/ml for both endoscopic and histological response [42].

Finally, further data about histological remission are awaited from the ongoing Intensive Treatment to Reach the Target with golimumab in moderate to severe UC patients treated with golimumab (IN-TARGET) (*clinicaltrials.gov* NCT02425865). This is a multicenter trial that will evaluate, as a secondary objective, histological remission at week 54 and 108. Recent data published taken from the VARSITY trial on patients with moderate to severe active UC, demonstrated the superiority of vedolizumab in comparison to adalimumab with respect to the achievement of clinical remission and endoscopic improvement [43]. Moreover, consistent with major outcomes, 10.4% of the patients in the vedolizumab group, compared with 3.1% in the adalimumab arm, achieved histologic remission at week 52 [43]. *Loftus et al.*, presented long-term outcomes of treatment with vedolizumab in their interim analysis of data from the continuing GEMINI extension study [44]. Concerning clinical remission, among patients with a clinical response at week 6 of treatment, 81% [114/140) maintained remission after 52 weeks, 88% (20/136) after 104 weeks and 96% (70/73) after 152 weeks [44]. Importantly, the authors showed an improvement in terms of quality of life in both disease-specific and global measures reported by patients treated with vedolizumab long-term [44].

As far as drug monitoring and immunogenicity are concerned, it was described in a recent cross-sectional study on IBD patients in maintenance therapy with vedolizumab, that, especially in UC patients, drug concentrations were significantly higher in corticosteroid-free and endoscopic remission

Table 2. Achievable targets in moderate to severe UC treated with biologics.

Reference	Investigated Target	Study Design	Intervention	Results
Nasuno *et al.* [34]	Clinical remission	Retrospective	Infliximab 5mg/kg	Patients in clinical remission (56/70) at 6 weeks remained in sustained clinical remission at 1 year; Steroid-free remission rate at 1 year was achieved by 43%
Magro *et al.* [21]	Histological remission	Prospective	Infliximab 5mg/kg	Sustained histological remission (Geboes index ≤ 3.0) at week 52 in about 66% of the patients in histological remission at week 8 and in about 83% of patients with histological remission at week 30
Tursi *et al.* [39]	Clinical, endoscopic and histological remission	Retrospective	Infliximab 5mg/kg	At 42-months of follow-up, 70.4% (*n*=118) of patients were in clinical remission. At 42-months of follow-up, 44.6% of the patients had MH and 24.2% had HH
Sugimoto *et al.* [40]	Clinical remission	Retrospective	Adalimumab	If clinical remission was achieved, the cumulative non-relapse rate at 6-years was 43.8%
Fernández-Blanco *et al.* [41]	Endoscopic and histological remission	Retrospective	Adalimumab	At week 8, 17.6% (*n*=34) of UC patients achieved histological remission (Geboes grade ≤ 3.0), at week 52, 26.5% had histological remission All patients who achieved histological remission also had mucosal healing
Sands *et al.* [43]	Clinical and endoscopic remission as major outcomes; Histological remission as adjunctive outcome	Randomized, controlled	Vedolizumab *vs*. Adalimumab	Vedolizumab was superior in comparison to adalimumab with respect to clinical remission and endoscopic improvement at week 52; 10.4% (*n*=386) of the patients treated with vedolizumab achieved histological remission
Loftus *et al.* [44]	Clinical remission	Prospective	Vedolizumab	Among patients in clinical response at week 6 of treatment, 81% [*n*=140) maintained remission after 52 weeks
Arijs *et al.* [46]	Endoscopic and histological remission	Prospective	Vedolizumab	58% (*n*=12) of patients with assessed endoscopic remission at week 52 achieved Histological remission as well; longer treatment was associated with deeper histological remission rates.

UC: ulcerative colitis; MH: mucosal healing; HH: histological healing.

(with a cut-off of 14.8 μg/ml at multivariate analysis, p=0.004) [45]; additionally, only 1.6% of patients developed anti-drug antibodies [45].

Targeting histological remission in patients treated with vedolizumab was described. *Arijs et al.*, followed up 41 patients from GEMINI I and GEMINI LTS treated with vedolizumab at three-time points (weeks 6, 12, 52): histological remission occurred in 58% (7/12) of patients with assessed endoscopic healing at week 52; longer treatment was associated with deeper histological remission rates [46].

No long-term data are available, so far, on Etrolizumab, that is currently under evaluation with respect to histological remission. *Peyrin-Biroulet et al.*, assessed 22% (21/97) of patients with moderate to severe active UC who achieved histologic remission (defined as resolution of neutrophilic inflammation) after 14 weeks of treatment with etrolizumab on biopsies from the open-label induction cohort of HICKORY trial [47].

3. REAL-WORLD PRACTICE

So far, the adoption of a T2T model in the real world is limited and still represents a challenge: data on T2T in UC in the daily practice is mainly derived from surveys. In a multicenter retrospective study on 246 UC patients in Southern Australia, clinicians' perceptions about clinical, endoscopic, and histological remission rate were significantly inconsistent with real-world data [48]. In detail, histological healing was indicated as "optimal treatment target" by 51% of clinicians [48]. Concerning outcomes, according to *Bryant et al.*, in real-life, clinical remission was achieved in 61% of patients, of whom 57% also had endoscopic remission (Mayo score ≤ 1). Moreover, combined clinical and endoscopic remission was reported in 35% of patients [48].

In a survey conducted among Dutch gastroenterologists, 76% of the participants indicated endoscopic remission alone, defined in the routine practice as endoscopic Mayo score less or equal to 1, as the main target in UC [49].

Furthermore, evidence of the long-term cost-effectiveness of T2T is crucial for the application of this strategy in the real world. Infliximab was identified as the best treatment option for inducing mucosal healing at 1-year with respect to cost-effectiveness in a recent analysis on adalimumab, IFX or vedolizumab as first-line treatment in biological-naïve patients with moderate-to-severe UC [50].

Nevertheless, data investigating the cost-effectiveness of a T2T strategy in UC is lacking. In Crohn's disease (CD) it has been demonstrated that targeting mucosal healing with IFX is a cost-effective strategy compared with targeting clinical remission over a 2-year period [51]. Similarly, a further cost-effectiveness analysis on Crohn's patients treated with adalimumab, based on the CALM indications, demonstrated that the T2T approach was cost-effective compared with clinical management [52]; in this study, a lower hospitalization rate and a more durable remission were associated to tight monitoring [52].

CONCLUSION AND FUTURE PERSPECTIVES

This review illustrates the present evidence on a T2T strategy in UC. Care for UC patients is extremely demanding, lifelong, comprehends expensive treatments and eventually surgery; therefore, a T2T method might be strongly beneficial for the management of the disease above all for improving long-term outcomes [17].

It must be underlined that monitoring is different from targeting; monitoring tools are instruments to let clinicians determine how far or close their patients are from the desired goal: importantly, according to STRIDE indication, biomarkers are not considered targets [2].

Currently, there are several targets in UC, divided into clinical, imaging, endoscopic and histological remission. The ease of the assessment of endoscopic activity through sigmoidoscopy, the uniform distribution of histologic lesions and the good correlation of biochemical markers might facilitate the application of the T2T strategy in UC, rather than in Crohn's disease. To date, imaging is not recommended for T2T in UC, even though bowel ultrasound (US) assessment is newly emerging as an option [53]. In the future, US might also be able to actively distinguish inflamed tissue from fibrosis, guiding with precise information on clinical decisions and after all surgical indications. The non-invasiveness and the low costs of US make this technique attractive. If the T2T will become the standard of care in IBD, considering the frequency of remission assessments in this model, valid alternatives to endoscopy will be required. Nevertheless, a consensus on the definition of 'imaging remission' in bowel US and further data about its impact on the natural history of the disease are awaited.

Intensification and optimization of the different therapy lines in UC change the natural history of the disease [30]. At present, approximately 10% of patients still require colectomy within 5 years after diagnosis [1, 10].

Efficient achievement of several targets has been demonstrated both for conventional and biologic therapies: 5-ASA compounds induce MH at 1-year follow-up after treatment with multimatrix mesalamine 2.4 g/day in 76.4% of the cases [28] and histological improvement in the long-term is possible in 59.7% of patients [29]; several clinical trials have assessed histological healing rates for IFX by 58% after at least 11 months of treatment [54] and by 55% for vedolizumab, with maximal efficacy after a longer treatment course (week 52) [46].

Since histological remission seems to occur with a certain delay compared to endoscopic remission, if additional evidence would confirm this feature, modifying monitoring time schedules and algorithms in a T2T direction will be imperative.

An extensive and long-lasting UC doubles the risk of developing CRC [11]: missing the target means allowing sustained inflammation, through pro-inflammatory cytokines IL-1 and TNF-a to interact with carcinogenic patterns (*i.e.* p53, DNA damage, DNA mismatch repair genes and base-excision repair) [11, 55]. Thus, properly targeting means preventing bowel damage and dysfunction and, ultimately, tumor occurrence.

Nevertheless, introducing and implementing T2T in real-life clinical practice is limited by the diversity of studies designs and therapeutic outcomes. Data on the T2T model in the real world are still scanty. What emerges is that the integration of a T2T algorithm in everyday clinical practice is possibly prevented by the availability and costs of wider use of invasive and expensive procedures; in addition, this process requires the implementation of knowledge and education by clinicians.

To be included among important clinical targets in the long-term management of UC patients, disability and quality of life, as well as anemia must be mentioned [2, 56].

Monitoring tools such as FC and drug trough level determination are emerging as a possible implementation of a T2T strategy. In a meta-analysis, *Mosli et al.*, defined an optimal cut-off 50 ug/g for FC [57]; the true impact of FC in T2T with special concern on long-term outcomes and escalation of therapy is yet to be determined. With respect to emerging targets, histological healing seems to be close to being recognized. In a prospective study on mild to moderate UC treated with AZA and 5-ASA, 87% of the patients who achieved histological remission maintained clinical remission at 1 year of follow-up with statistical significance (p=0.006) [58]; yet, the process towards a more substantial level of evidence of this target has barely started and needs endorsement from meta-analyses.

Importantly, it must also be underlined that a T2T strategy might reveal limitations: *one size does not fit all* is particularly true for IBD. There is not a single UC but rather many; they differ in biology, progression and severity, as well as in drug responsiveness.

In the future, molecular remission might additionally emerge in UC: some authors already proposed the expression of LPHN2 and FGF7 as predictive markers of response to specific drug classes [46].

An efficient T2T strategy combining clinical and patient-reported outcomes (PROs) parameters together with non-invasive specific biomarkers of inflammation might reveal superiority to the standard strategy especially in mild to moderate UC. The results from the ongoing *OPTIMISE* trial

(*clinicaltrials.gov* NCT043340895) are warranted in order to add evidence to T2T strategy in the management of these patients.

In conclusion, evidence of T2T in UC needs to be endorsed by randomized clinical trials and, eventually, the revision of STRIDE guidelines is warranted; research should, furthermore, focus on mild to moderate disease, that, indeed, represents the vast majority of patients.

CONTRIBUTION OF AUTHORS

S Danese has served as a speaker, consultant and advisory board member for Schering- Plough, AbbVie, MSD, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alphawasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor and Johnson & Johnson, Nikkiso Europe GMBH, Theravance. G Roda has served as speaker for Abbvie, Takeda, Pfizer. M Argollo has served as a speaker, consultant and advisory board for Abbvie, Janssen, Takeda, Pfizer. LP Biroulet has served as a speaker, consultant and advisory board member for Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC- Pharma, Index Pharmaceuticals, Amgen, Sandoz, For- ward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, Theravance. K Peridaens is an employee of Ferring Pharmaceuticals.

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