Development of a Software for Treat-To-Target Strategy Implementation and Increasing Quality of Life in Patients with Inflammatory Bowel Disease

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ABSTRACT: The management of each form of the inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn’s disease (CD), represents a challenge for the clinician and patient. The treatment paradigm was shifted from achievement of a symptomatic control of the disease, to the prevention of bowel damage, disease progression and disability, and better quality of life. These goals were related with the treat-to-target (T2T) strategies developed for a proper treatment optimization. The T2T strategy is based on the assessments of the biochemical markers (C-Reactive Protein-CRP and fecal calprotectin-FCAL), clinical targets (multiple clinical scoring systems), endoscopic targets (resolution of ulceration and friability, and histologic targets. Another objective of the treatment is the obtaining of a higher level of improvement for the patient’s quality of life (QoL). One of the most reliable ways for a better management of IBD is represented by the IT instruments. In this respect, we developed under the auspices of RCCC (Romanian Club of Crohn’s and Colitis) between 2018-2019 a new software for collecting medical data of IBD patients, according to STRIDE recommendations, in order to have continuous access to their evolutionary history and all therapeutically aspects. The software proved to be a valuable tool for clinician with a positive impact on clinical, economic, and patient-centred outcomes in IBD.

KEYWORDS: Inflammatory bowel disease, disease management, software for collecting medical data.

Background

Inflammatory bowel disease (IBD) represents a chronic, relapsing, and remitting inflammatory condition of the gastrointestinal tract, and includes two forms with different pathology and clinical characteristics: ulcerative colitis (UC) and Crohn’s disease (CD).

By far, the etiology and pathogenesis of these disorders are still poorly understood, being involved at least two different mechanisms, genetic and environmental [1].

Being studied for more than 50 years, IBD became an important issue both for gastroenterology and public health, due to their clinical, psycho-social, and economical consequences.

Recent studies (Global Burden of Diseases, Injuries, and Risk Factors Study-GBD-2017) [2] have proved that their burden is rising with an estimated 6-8 million cases globally, with an age-standardized prevalence rate that reached 84.3/100,000 inhabitants, while the age-standardized death rate decreased in the last 30 years to 0.51/100,000 populations.

In Romania, data from 2004 revealed that the incidence in the referral population was 0.97/100,000 for UC and 0.50/100,000 for CD, whereas the prevalence rate was 2.42/100,000 for UC, respectively 1.51/100,000 for CD [3].

Regarding the perceived burden of IBD, same GBD study has underlined that the Years Lived with Disability (YLDs) attributed to IBD almost doubled during a 30 years period, from 0.56 million in 1990 to 1.02 million in 2017, while in the same time, the age-standardized rate of DALYs has decreased 23.2 [2].

These data reveals the importance of IBD’s burden and also the need of development for new therapeutically strategies and management processes in order to lead to a decrease of the substantial social and economic impact of IBD in the future.

Initially, the treatment of IBD was orientated towards achievement of a symptomatic control of the disease, based on clinical parameters. In IBD, the correlation between clinical symptoms and endoscopic or histological disease was proved to be a weak one, many patients presenting symptoms although mucosal and histological healing is present and vice versa [4].

This issue was mostly revealed during the SONIC trial, where half of the patients had evidence of residual disease activity, according to endoscopic and/or C-reactive protein (CRP)
assessment, even if they were considered in clinical remission, whereas the other half of patients still had persistent clinical symptoms despite evidences of an endoscopic and CRP normalization [5].

Comparing UC to CD, for patients within first category the endoscopic activity was better correlated with symptoms, although many of them were in clinical remission expressed through normalization of stool frequency, but still has endoscopic activity [6].

Once immunomodulators (azathioprine) and the anti-tumor necrosis factor (TNF) gained their place on the therapy, the treatment paradigms in IBD has changed, being guided more by more robust objectives [7,8] and aiming to prevent bowel damage, disease progression and disability and increase life quality.

**Treat-to-target strategy**

The treat-to-target strategies were introduced in order to fulfill the IBD consensus recommendation on selecting therapeutic targets, according to which the objectives of treatment were shifted from only symptomatic disease control to a support targeting composite therapeutic outcome, periodically assessed.

The concept of treat-to-target (T2T) has evolved from therapeutically experience in other chronic diseases, such as diabetes or rheumatoid arthritis, and has proved to lead to improved outcomes.

In IBD, T2T was developed by the selecting therapeutic targets in inflammatory bowel disease (STRIDE) committee, an international expert panel organized in 2015 under the auspices of the International Organization for the Study of Inflammatory Bowel Diseases.

According to the principles of the T2T concept, the therapeutically process needs a predefined goal centered on the patient’s individual needs, regularly assessed and adjusted for a proper treatment optimization [9].

The treat-to-target recommendations for CD comprised composite endpoints of clinical and endoscopic remission, including resolution of abdominal pain and damaged bowel, as well as resolution of ulceration, monitored through ileocolonoscopy or cross-sectional imaging.

In the case of UC, the clinical criteria of treat-to-target were related to resolution of rectal bleeding and also normalization of bowel habit, while endoscopic assessment needs to prove the resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy [9].

In the early stages of T2T strategy development, for both diagnoses (CD and UC), STRIDE committee did not consider the biochemical markers and histopathology as adjunctive endpoints.

After a couple of years, the results of CALM trial had showed that became important to conduct a tight disease monitoring using markers of inflammation and precocious treatment intervention, in order to obtain better outcomes of the therapeutic management [10].

Based on these evidences, the STRIDE created the concept of tight disease control, as one of the most important ways of timely assessment of disease activity, being described as a management approach in which every therapeutically decisions needs to be justified by a close monitoring of outcome measures, in order to obtain the improvement of patient clinical status.

The benefits of tight control were emphasized by two other studies in which treatment for IBD was guided by biomarkers, such as CRP and fecal calprotectin (FCAL) [11,12], as long as these two are the most extensively investigated non-invasive markers of inflammation in IBD, compared to more invasive and costly procedures to measurement of inflammatory activity, such as ileocolonoscopy or cross-sectional imaging.

Thus, according to the expert consensus, tight control is based on different therapeutic target, each of that having its role in the process of disease management.

In the spectrum of clinical targets, the symptoms of disease need to be constantly monitored through multiple clinical scoring systems such as Crohn’s Disease Activity Index (CDAI) and Harvey Bradshaw Index (HBI) for CD, respectively Mayo score (Mayo) and the Simple Clinical Colitis Activity Index in UC [13-16].

As long as all these scoring systems are composites ones, mostly relying on clinician’s point of view and according to the STRIDE recommendations, the resolution of clinical symptoms constitute a distinct therapeutic target; it became necessarily to use a new assessment tool, based on patient’s perspective about symptoms and therapy’s results.

Thus, was developed the Patient Reported Outcome (PRO) that evaluates, based on each patient’s own perspective, the resolution of abdominal pain and normalization of bowel habit in CD, and resolution of rectal bleeding and normalization of bowel habit in UC [17].
To obtain the proper results of tight control, it is necessary to use PRO tools periodically at every three months during active disease, and every six to twelve months after symptom remission [9].

As mentioned above, the biochemical targets of tight control are expressed through the most used biomarkers, such as serum CRP and FCAL, their higher levels being associated with inflammation related to clinical disease activity in both UC and CD [18,19].

Regarding the cut-off levels for FCAL, there were different studies that proposed values varying between 250ug/g-300ug/g, and bigger values over the cut-off point was valued as predictor both of disease flare, the higher scores being usually recorded in the 3 months before the endoscopic findings [20,21].

Even if the CRP and/or FCAL are non-invasive and not expensive, due to lack of sufficient evidences STRIDE did not include them among recommendations, but were included as adjunctive measures that could be very useful to set an optimal timing of endoscopy [9].

Endoscopic targets were considered by the STRIDE recommendation as long as numerous studies have proved that the improvement of disease’s evolution is directly related to mucosal healing.

Thus, it was observed that the periodical endoscopic monitoring was associated with long-term clinical and corticosteroid-free remission, lower rates of surgery and hospital admissions, becoming the background of treatment optimizations [22-27].

The STRIDE expert consensus proposed as endoscopic component of tight disease control a resolution of ulceration at six to nine months after the start of treatment in CD, and resolution of ulceration and friability in UC, as evaluated after three to six months the onset of therapy [9].

The assessment of endoscopic targets is usually reflected through Mayo score and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) for UC, respectively Endoscopic Index of Severity (CDEIS) and Simple Endoscopic Score for Crohn’s disease (SES-CD) for CD, but despite the fact that there are not settled any cut-off values for these scores in order to define optimal mucosal healing, however STRIDE recommendations and International Organization for the Study of Inflammatory Bowel Disease (IOIBD) suggested a decrease of CDEIS bigger than 50% and a Mayo score between 0 and 1 as criteria for remission [9,28-30].

Another set of criteria discussed in the treat-to-target strategy are histologic targets, but the microscopically assessment of the colonic mucosa did not reach enough evidences to support it as a treatment target and thus, as a recommendation for STRIDE.

Same issue regarding lack of evidences it was behind the STRIDE decision to consider imaging modalities as a complementary method used in evaluation of lesion’s resolution in patients with CD [31,32], while for UC the cross-sectional imaging modalities are not recommended at all [9].

Quality of life in IBD patients

An important goal for both STRIDE recommendations and treat-to-target strategies is to attain a higher level of improvement of the patient’s quality of life (QoL).

It was showed that QoL represents a deeply subjective concept related to a personal reflection of the severity of symptoms and their consequences on the patient’s everyday life.

Moreover, in case of IBD, the way to assess the symptoms and disease’s evolution contribute also, through the level of invasiveness, to a more negative perceived impact on individual’s life [33].

In the last several years, it was also proved that a better and individualized therapeutic management of IBDs is the way to obtain a deep remission and, accordingly a better QoL [10].

It is important to underline that IBD has not only a clinical picture, but also a complex psychological and social background, which needs to be included in the process of treatment and recovery.

In this respect, in order to avoid the patient’s noncompliance and to improve the self-management, it becomes necessarily to involve the patient in the decisional process regarding the treatment targets and appropriate ways to reach these goals [34,35].

The psychological part of the IBD has a crucial influence on the management, starting from difficulties to accept and to discuss about the disease, to discomfort, irritability, chronic pain, and fatigue, and even psychiatric disorders such as anxiety, depression [36].

It is also important to add to the psychosocial impact of IBD the perceived stigmatization of individuals affected, which directly influence the level of disease management [37], in the sense of a poor adjustment not only to the clinical
reality of the disease, but also to the psychosocial condition associated to IBDs [38].

Even if, as mentioned above, the QoL is an important goal of therapeutically process of IBD, actually it was proved that in the daily practices there are many challenges to assess and to improve QoL, due to lack of standardized tools and difficulties to measure and illustrate a very subjective concept.

Since the QoL has gained such weight, there were developed instruments to evaluate it like Inflammatory Bowel Disease Questionnaire [39] or IBD disability index [40].

As long as the self-perceived QoL has become a pillar of the Patient Reported Outcome (PRO), it was introduced as a research item on IBD clinical trials [41,42] for measuring the level of disability induced by the disease and correlated with other variables like drug compliance, stigma, or social functioning.

IT tool for treat-to-target implementation in medical practice

The complexity of IBD as presented above, has led to the necessity of a comprehensive management in which clinical, psycho-social, environmental and even economical components have their important role.

A possible solution to that is to develop and implement a technological tool for collecting, aggregating and computing all medical data available for the patients with IBD, in order to obtain a widest and clearer view of them at a specific moment.

Thus, one of the proposed IT instruments developed to fill the technological gap in the management of IBD is the software initiated by the RCCC (Romanian Club of Crohn’s and Colitis) and developed in our center. During the 2018-2019 period, the RCCC experts have discussed about the need of a new software, a friendly and comprehensive one (Fig.1, Fig.2), about the clinical and non-clinical items to be included in the application’s database and the proper way in which results are graphically resumed (Hemoglobin, Erythrocyte Sedimentation Rate, C-Reactive Protein, Calprotectin, Endoscopic Score, Patient Weight, General Score appreciated by the patient).

The software has the possibility for each user login and to export all data into Microsoft Excel for complex statistical analysis.

![Fig.1. General interface of the IT program after a user login.](image)
The objectives of this application were to collect medical data of IBD patients in order to achieve the prerequisites of treat-to-target (T2T) and to have continuous access to the patient’s IBD evolutionary history and all therapeutically aspects (Fig. 3).

Once having all these data, the role of software is to compute them based on an algorithm developed according to STRIDE recommendations and present guidelines, and to offer the proper timing for any clinical and therapeutic decision.

The whole process will lead to an improved tight control of the disease, better compliance to therapy and, finally, to an increased quality of life.
Conclusion
Based on the experience of using the software and on the positive outcomes obtained after, we could sustain that this IT application is a valuable tool for clinician, offering him an amount of essential medical data that are covering the whole STRIDE recommendations, in the minimum time, effortless and in a friendly virtual environment.

Also, it was proved that using the software for a T2T approach had a positive impact on clinical, economic, and patient-centred outcomes in IBD.

The goals of better compliance and adherence to treatment, patient engagement in therapeutic management and increased quality of life are easily to be obtained having a computer-based solution that offers all necessarily data to reach the window of opportunity in treatment.

Conflict of interests
None to declare.

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