

Mild-to-moderate IBD management: Challenges beyond inflammation

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Gerhard Rogler, Ian Arnott, Prof. Jonas Halfvarson © Tillotts Pharma

The satellite symposium sponsored by Tillotts Pharma was introduced by the Chair, Prof. Gerhard Rogler, Zürich, Switzerland. He briefly highlighted the treatment paradigm and treatment goals of ulcerative colitis (UC), the challenges of treating the elderly and the use of patient reported outcomes (PROs) in inflammatory bowel disease (IBD).

The text below is a summary of the presentations of the three speakers.

Treatment of UC

Treatment strategies in UC are dependent on the disease severity. The ECCO guideline on the diagnosis and management of UC [1] considers mesalazine as the gold standard for the treatment of mild-to-moderate UC, with more severe UC cases being treated with corticosteroids and biologics. Regardless of the disease severity, the treatment goals in UC remain the same; these include reducing mortality, number of colectomies and hospital admissions, whilst optimising treatment adherence, surveillance/monitoring, and most importantly inducing mucosal healing.

Clinical trials tend to exclude elderly patients, thus presenting challenges to treating physicians with respect to treating this population.

Patient reported outcomes (PROs)

The patient's and the physician's perspectives on disease severity and activity often do not correlate. There is the opinion of the regulators that physician reported outcomes do not reflect the patient's disease burden; hence PROs are becoming more widely applied in the assessment of disease activity.

The advantages of PROs are that they engage patients in their disease management (i.e., providing a sense of empowerment), leading to bidirectional communication and educating patients and physicians to speak a common language. In contrast, the disadvantages are that PROs are currently not well-validated in clinical trials, comparison to efficacy data from older trials is no longer possible and lastly, PROs are subjective by definition. These topics were discussed in more detail by Dr. Ian Arnott, Edinburgh, Scotland and Prof. Jonas Halfvarson, Örebro, Sweden.

Treatment of mild-to-moderate IBD in the elderly

Ian Arnott, Edinburgh, Scotland

Trends in the elderly population

Based on current trends, it is predicted that between 2012 and 2032 for those aged 65-84 and 85+ years, the UK will see a population increase of 39% and 106%, respectively [2, 3]. With an estimated 10-30% of the IBD population aged over 60 years [4] this equates to an increased number of elderly IBD patients who will need treatment in the years ahead. The elderly population are composed of those who have received a diagnosis of IBD later on in life (elderly-onset IBD), and those who have had IBD for several decades. Both elderly groups present the physician with unique challenges for the management of their IBD.

Case study presentation

The following case study was presented: Mr. RF, a male (non-smoker) aged 68 years, presented in 2008 with a four-week history of bloody diarrhoea, bowel movements 5-6x/24 h, he had no nocturnal symptoms and no abdominal pain. Past medical history included mild asthma and depression. Hb 104 g/L (slightly anaemic), MCV 76.3, WCC 10.6, Platelets 355, Albumin 32, and CRP 6.

The varied voting responses of the audience to the question "What is the correct diagnosis? (a) diverticular disease, (b) colon cancer, (c) inflammatory bowel disease" highlighted that many physicians make different plausible diagnoses; reflecting the everyday challenges in the treatment of elderly IBD patients.

The audience learned that Mr. RF underwent sigmoidoscopy, which resulted in the diagnosis of rectosigmoid UC.

Challenges with the treatment of elderly IBD patients

Due to the high probability of polypharmacy, the potential for drug interactions is higher in elderly IBD patients. Diagnosis of IBD in elderly patients is often not as straightforward as in younger patients; this is due to IBD being confused with other diseases such as ischemic colitis, infective colitis, microscopic colitis, diverticular disease and IBS to name a few [4].

The delay in diagnosis has been reported to be longer in the elderly (15 months vs. 5 months) [5] and IBD specific mortality is higher in this group; with the leading cause of death being due to solid malignancies [6]. As elderly IBD patients can be affected by unrelated diseases and health problems, it is important that all relevant specialists talk to each other. For example, in elderly patients with diabetes; the use of steroids may alter glycaemic control, whilst psychiatric disorders may have an effect on medication compliance.

The clinical course tends to be mild in elderly-onset IBD patients, with less presentation of abdominal pain and weight loss, lower frequency of fistulising disease and family history. In Crohn's disease (CD), there tends to be a higher percentage of colonic disease, and in UC, left-sided colitis is the most typical phenotype

Therapeutic considerations for the elderly

The discussion of the case study continued with the question: "What treatment should be given now? (a) 5-ASA, (b) corticosteroids (with/without 5-ASA), (c) immunomodulators/biologics".

Dr. Arnott highlighted that mesalazine, corticosteroids, immunomodulators and surgery are potential treatment options for the elderly IBD population as detailed below.

Mesalazine [1, 7, 8]:

- First drug of choice in the treatment of mild-to-moderate UC.
- Mesalazine is effective for inducing and maintaining remission in UC. Efficacy is comparable between young and older patients.
- Once daily dosing and foam formulations of topical therapy may increase compliance.
- Creatinine clearance should be monitored regularly during therapy (particularly in case of long-term high dose usage).
- Drug interactions with warfarin, 6-mercaptopurine and azathioprine should be considered.

Corticosteroids [9, 10]:

- Use of corticosteroids carries the risk of precipitating/exacerbating pre-existing conditions (e.g. diabetes, congestive heart failure, hypertension, altered mental status and osteoporosis) – more frequent compared to a younger population.
- Bone densitometry needs to be repeated annually.
- Budesonide might be considered as it interferes less with bone metabolism.
- Potential drug interactions include: phenytoin, phenobarbital, ephedrine and rifampicin.

Immunomodulators [10-12]:

- Should be considered in patients with corticosteroid dependence to maintain patients in remission.
- Age is a risk factor for skin cancer and lymphoma in patients exposed to thiopurines.
- Allopurinol could potentially reduce the thiopurine dose (however its concomitant use with immunomodulators increases the risk for infections in those patients with lower absolute lymphocyte counts).

Surgery [13, 14]:

- About 25% of IBD surgeries are performed in patients >55 years of age.
- Older age is associated with an 8-fold increased risk of in-hospital post-operative mortality (leading causes include sepsis and bowel perforation) and higher post-operative morbidity.

Case study continued

The audience learned that Mr. RF was treated with 2 g mesalazine liquid enema. He initially had a good response, and his faecal calprotectin (FC) was 140 µg/g. In December 2008 (due to no response), 2.4 g/day oral mesalazine was added to his treatment regimen, and increased to 4.8 g/day four weeks later. In January 2009 (again due to no response), he underwent a four-week course of corticosteroids, followed by tapering off for two weeks. In mid-March 2009, Mr. RF was in steroid-free remission; he had no rectal bleeding, his Ulcerative Colitis-Disease Activity Index score was less than 2, with a Mayo endoscopic subscore of 0. Subsequently, his treatment was reduced to 1.6 g/day mesalazine.

Conclusions: Therapeutic strategy in the elderly

Dr. Ian Arnott concluded that a bottom-up approach (e.g. mesalazine > corticosteroids > thiopurines > biologic therapy) is the preferred therapeutic strategy in the elderly. He emphasised that one should be cautious with using biologic therapy (e.g. anti TNFs) in the elderly as this is associated with a risk of severe infections.

Relevance of PROs and biomarkers in clinical practice

Jonas Halfvarson, Örebro, Sweden

Patient reported outcomes (PROs)

PROs are becoming an important aspect of assessing disease activity of IBD, with both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) acknowledging the need to accurately measure both the patient's experience of the disease and the biological manifestations of the disease.

PROs according to the EMA:

- any outcome evaluated directly by the patient themselves and based on the patient's perception of a disease and its treatment.
- PRO is an umbrella term covering both single dimension and
- multi-dimension measures of symptoms, HR-QoL, health status, adherence to treatment, satisfaction with treatment, etc.

PROs according to the FDA:

- any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.
- The outcome can be measured in absolute terms (e.g. severity of a symptom, sign or state of a disease) or as a change from a previous measure.

Why use PROs?

In the study by Schreiber et al. 2013, patients and physicians were asked to rate the severity of their/the patient's disease. In this study, patient disease severity was classified as milder by the physician, in comparison to the view of the patient [15]. This highlights that patient's and physician's perspectives do not necessarily correlate; with physicians potentially under-

estimating the severity of the patients' problems, or over-estimating the treatment improvement.

PROs are a relatively new concept; they should be valid, reliable, responsible and feasible.

The following are examples of PROs in CD and UC:

- PRO-2 [CD] [16] – the clinical target based on the Crohn's Disease Activity Index is:
 - Resolution of abdominal pain (abdominal pain ≤1)
 - Normalisation of bowel habit (mean daily stool frequency ≤1.5)
- PRO-2 [UC] [17] – the clinical target based on the Mayo score is:
 - Resolution of rectal bleeding (rectal bleeding = 0)
 - Normalisation of bowel habit (stool frequency ≤1)

Confirming disease activity

As patients rarely accept repeated colonoscopies, biomarkers can be measured in conjunction with PROs to confirm disease activity. Examples of biomarkers of IBD disease activity include FC and C-reactive protein (CRP).

FC is a promising biomarker for the diagnosis of IBD; a meta-analysis of 13 studies (including 744 UC and 727 CD patients) demonstrated that endoscopic healing in IBD patients can be determined by the assessment of FC [18].

CRP levels are often used in the follow-up of patients with IBD. A study by Henriksen et al., 2008, demonstrated that CRP levels at diagnosis were related to the extent of disease in patients with UC. [19].

Treat to target (PROs and Biomarkers)

The Selecting Therapeutic Targets in IBD (STRIDE) program developed by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) [20] examined potential treatment targets for IBD to be used for a "treat-to-target" clinical management strategy. With regards to PROs and biomarkers STRIDE recommends the following:

Composite endpoints for CD:

- PRO remission (resolution of abdominal pain and diarrhoea/altered bowel habit) to be assessed at a minimum of 3 months during active disease.
- Endoscopic remission (resolution of ulceration at ileocolonoscopy or resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy) to be assessed at 6-9 months intervals during active disease.

Composite endpoints for UC:

- PRO remission (resolution of rectal bleeding and diarrhoea/altered bowel habit).
- Endoscopic remission (resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy).
 - To be assessed at a minimum of 3 months interval during active disease.

Biomarkers:

- Available biomarkers, including CRP and FC, are not treatment targets because there is insufficient evidence to recommend treatment optimisation using biomarkers alone.

Case study conclusion

Mr. RF had a FC of ~100 µg/g until December 2009 (tested monthly until April 2009, and then every two months), with PRO-2 showing increased stool frequency (3/day).

The audience were asked "What will you do? (a) Keep monitoring F-calprotectin and PRO 2, (b) nothing, or (c) increase the treatment dose from 1.6 g/day to 2.4 g/day 5 ASA". Most of the audience responded equally with (a)

and (c). In response to the voting, Prof. Gerhard Rogler commented that it is important to treat the symptoms and hence he would advise to increase the dose of mesalazine.

In the case of Mr. RF, he was just monitored, and his stool frequency reverted to normal. After additional 6 months, the FC increased progressively to 280 µg/g, whilst no changes in PRO-2 were observed. The audience were asked "What will you do? (a) keep monitoring FC, (b) schedule for endoscopy, or (c) increase the treatment dose of 5-ASA from 1.6 g/day to 2.4 g/day". The majority of the audience voted to schedule for an endoscopy.

Conclusions

Elderly IBD patients are a growing patient population. Physicians need to take into account comorbidity, polypharmacy and cognitive decline when deciding on IBD treatment strategy. Finally, PROs and biomarkers are becoming increasingly important in the assessment of disease activity.

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