Inflammatory bowel disease in older patients: from gut feeling towards evidence-based medicine

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General introduction and outline

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease, comprising Crohn's disease (CD), ulcerative colitis (UC) and IBD-Unclassified (IBD-U).[1] Circa 87.000 individuals are diagnosed with IBD in the Netherlands.[2] IBD is characterized by a relapsing and remitting inflammation of the intestines and patients often present with disabling symptoms such as abdominal pain, (bloody) diarrhoea and fatigue, reducing quality of life.[1] Diagnosis is based on the presence of symptoms, physical examination, blood tests and endoscopy or additional imaging.[3]

IBD is incurable and treatment consists of two pillars: remission induction and maintenance therapy. During a relapse of disease, remission induction is necessary and mainly attempted to achieve by prescribing corticosteroids. After remission induction is reached, tapering off corticosteroids is essential due to their unfavourable safety profile. During maintenance therapy which is often started directly after or during induction therapy, preserving remission and preventing recurrent disease activity are aimed for. Treatment goals can be divided into clinical remission, biochemical and endoscopic (macroscopic inflammation) remission and mucosal healing (microscopic inflammation).[4]

The first step of medical therapy consists of mesalamine or budesonide (in UC) and budesonide without maintenance therapy (in CD). Second line treatment involves systemic steroids and immunomodulators such as thiopurines or methotrexate. The third line consists of biologicals: anti-TNF therapy such as infliximab or adalimumab, ustekinumab or vedolizumab and the more recently available small molecule tofacitinib.[4-6] In general, preference towards surgical therapy is only given in case of lack of response to medical therapy.[7 8]

OLDER PATIENTS WITH INFLAMMATORY BOWEL DISEASE

The population of older patients with IBD, often defined as aged 65 years or older, is increasing. It is estimated that in the next decade more than one-third of all IBD patients will be older adults.[9] A rising prevalence due to ageing of the general population and a rising incidence of IBD in older adults has been observed. The latter could be due to increased use of diagnostic tools for example in the context of colorectal cancer screening. It also has been speculated that decreased microbial diversity and pathophysiologic alterations including cellular senescence and chronic inflammation in older adults play a role in the increased incidence.[10-13]

Older patients with IBD experience a higher risk of negative health outcomes. A higher frequency of IBD-related hospitalization and a higher risk of developing serious adverse events during treatment, such as infections or lymphoproliferative disorders, and the need

for surgery, as compared to younger patients has been observed.[14] Although guidelines do not advise different treatment strategies in older patients as compared to younger patients, several studies have shown that older patients are being treated differently in daily clinical practice. Diagnosis at an older age is associated with lower use of corticosteroid sparing therapies such as immunomodulators and biologics compared with a younger age.[15 16] Besides, older patients more often receive longer courses of corticosteroid therapy and in higher doses.[15-17] The above mentioned differences in treatment are not necessarily due to a milder disease course in older patients[15] and could be due to patient-related factors such as comorbidity and frailty, which are more often present in older patients. Up until now, it has not been clear which considerations from professionals and patients underlie these differences in therapy choices and if these considerations are supported by any evidence.

COMORBIDITY, GERIATRIC CONDITIONS AND FRAILTY

Healthcare in older patients is often challenging due to the presence of multimorbidity. In over two-third of adults aged 65 years or older, two or more chronic morbidities are present.[18] IBD patients are exposed to an even higher risk of morbidity as compared to non-IBD patients due to the chronically present inflammation and medication used.[19 20] However, in randomized clinical trials researching new medications, patients with IBD with significant comorbidities fail to meet the strict inclusion criteria. Especially regarding treatment with recently introduced biologicals or small molecules, it is unknown what the impact of comorbidities is on treatment outcomes.

A higher age is also associated with the presence of geriatric conditions. Geriatric conditions, such as cognitive impairment or a history of falls, are not automatically related to a specific disease or (co-)morbidity.[21] A comprehensive geriatric assessment is used to assess these conditions. This assessment is defined as a multidisciplinary evaluation in which problems are uncovered and resources and strengths of the patient are defined.[22] It includes a geriatric assessment which explores four different domains, namely the somatic, functional, mental and social domain. The somatic domain includes assessment of (co-)morbidities, polypharmacy and malnutrition. This domain is usually included as a part of routine care. The functional domain includes functional performance, measured by the level of independence in (instrumental) activities of daily living, and level of physical capacity, for example measured by gait speed or handgrip strength. The mental domain includes cognitive performance and depression, the social domain includes the evaluation of the social support network.[22] During a comprehensive geriatric assessment, the findings of this geriatric assessment are evaluated by a multidisciplinary team often led by a geriatrician and among others a specialist elderly care nurse and a physiotherapist. The process of a comprehensive geriatric assessment, which is often closely linked with interventions, has been proven effective in the field of oncology as it predicts cancer treatment tolerance, mortality and enhances quality of life and leads to a reduction in the number of invasive treatments performed.[23-25]

The above-mentioned assessment can be integrated into an overall level of frailty. Frailty is defined as a state of increased vulnerability to poor resolution of homeostasis following a stress. There are many ways of measuring frailty, however, a geriatric assessment is considered to be the gold standard.[26] Because a geriatric assessment is a time consuming effort, patients are often screened for frailty prior to an assessment. Based on findings of this screening, the more detailed assessment can be undertaken.[22]

Thus, the difference between older and younger patients does not primarily lie in the age itself, but rather in heterogeneities concerning comorbidities, geriatric conditions and level of frailty. Because of the presence of these heterogeneities, treating the population of older patients with IBD can be challenging. In other medical fields, research performed in older patients shows an association between the presence of frailty and adverse health outcomes, thereby presenting the use of frailty screening or a comprehensive geriatric assessment as a valuable tool in clinical decision making.[27,28] However, in IBD this is still an unexplored subject.

This thesis therefore has three aims:

I) To research factors contributing to current therapy choices and treatment goals in older patients with IBD accounting for the perspectives of both professionals and patients, and to quantify the current evidence on geriatric assessment and its relation with health outcomes.

II) To study the association between comorbidity, prior to start of medical therapy, and safety and effectiveness outcomes in patients with IBD.

III) To assess the prevalence of frailty in older patients with IBD and its association with health outcomes over time.

THESIS OUTLINE

This thesis starts by evaluating underlying considerations which can contribute to the disparities in treatment of older patients as compared to adult patients with IBD by using qualitative methods, interviewing both professionals and patients. The results are presented in **Chapter 2**. This chapter also explores the relationship between frailty and therapy goals in IBD treatment in current practice. **Chapter 3** quantifies the current evidence on geriatric assessment and its association with adverse health outcomes in IBD patients by performing a systematic literature review. **Chapter 4** describes the association between comorbidities prior to start of anti-TNF therapy and safety and effectiveness outcomes, **Chapter 5** describes the association between comorbidities prior to start of ustekinumab or vedolizumab therapy and safety and effectiveness outcomes, both by using real world data. **Chapter 6** describes the prevalence of deficits in geriatric assessment in a multicentre cohort of older patients with IBD. In addition, this chapter looks into the association between deficits in a geriatric assessment, disease activity and disease burden. **Chapter 7** studies the longitudinal relation between frailty screening, geriatric assessment and hospitalization after 18 months in the same cohort, thereby researching the value of frailty screening as a clinically applicable risk stratification in the treatment of older patients with IBD. Finally, in **Chapter 8** the overall findings of this thesis are summarized, clinical implications are discussed, and future research ideas proposed.

REFERENCES

1. Cosnes J, Gower-Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;140(6):1785-94. doi: 10.1053/j.gastro.2011.01.055 [published Online First: 2011/05/03]
2. Spekhorst LM, Imhann F, Festen EAM, et al. Cohort profile: design and first results of the Dutch IBD Biobank: a prospective, nationwide biobank of patients with inflammatory bowel disease. *BMJ Open* 2017;7(11):e016695. doi: 10.1136/bmjopen-2017-016695 [published Online First: 2017/11/11]
3. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1989;170:2-6; discussion 16-9. [published Online First: 1989/01/01]
4. Handleiding behandeling IBD 2014-2015. *Initiatief in Crohn en Colitis*
5. Torres J, Bonovas S, Doherty G, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis* 2020;14(1):4-22. doi: 10.1093/ecco-jcc/jjz180 [published Online First: 2019/11/12]
6. Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis* 2017;11(7):769-84. doi: 10.1093/ecco-jcc/jjx009 [published Online First: 2017/05/18]
7. Oresland T, Bemelman WA, Sampietro GM, et al. European evidence based consensus on surgery for ulcerative colitis. *J Crohns Colitis* 2015;9(1):4-25. doi: 10.1016/j.crohns.2014.08.012 [published Online First: 2014/10/12]
8. Bemelman WA, Warusavitarne J, Sampietro GM, et al. ECCO-ESCP Consensus on Surgery for Crohn's Disease. *J Crohns Colitis* 2018;12(1):1-16. doi: 10.1093/ecco-jcc/jjx061 [published Online First: 2017/05/13]
9. Coward S, Clement F, Benchimol EI, et al. Past and Future Burden of Inflammatory Bowel Diseases Based on Modeling of Population-Based Data. *Gastroenterology* 2019;156(5):1345-53 e4. doi: 10.1053/j.gastro.2019.01.002 [published Online First: 2019/01/15]
10. Jeuring SF, van den Heuvel TR, Zeegers MP, et al. Epidemiology and Long-term Outcome of Inflammatory Bowel Disease Diagnosed at Elderly Age-An Increasing Distinct Entity? *Inflamm Bowel Dis* 2016;22(6):1425-34. doi: 10.1097/MIB.0000000000000738 [published Online First: 2016/03/05]
11. United Nations. World Population Ageing, 2019: Highlights. New York, NY: United Nations publication; 2019.
12. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;142(1):46-54 e42; quiz e30. doi: 10.1053/j.gastro.2011.10.001 [published Online First: 2011/10/18]
13. Hong SJ, Katz S. The elderly IBD patient in the modern era: changing paradigms in risk stratification and therapeutic management. *Therap Adv Gastroenterol* 2021;14:17562848211023399. doi: 10.1177/17562848211023399 [published Online First: 2021/07/20]
14. Sturm A, Maaser C, Mendall M, et al. European Crohn's and Colitis Organisation Topical Review on IBD in the Elderly. *J Crohns Colitis* 2017;11(3):263-73. doi: 10.1093/ecco-jcc/jjw188 [published Online First: 2016/11/01]
15. Everhov AH, Halfvarson J, Myrelid P, et al. Incidence and Treatment of Patients Diagnosed With Inflammatory Bowel Diseases at 60 Years or Older in Sweden. *Gastroenterology* 2018;154(3):518-28 e15. doi: 10.1053/j.gastro.2017.10.034 [published Online First: 2017/11/06]
16. Govani SM, Wiitala WL, Stidham RW, et al. Age Disparities in the Use of Steroid-sparing Therapy for Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2016;22(8):1923-8. doi: 10.1097/MIB.0000000000000817 [published Online First: 2016/07/15]

17. Johnson SL, Bartels CM, Palta M, et al. Biological and steroid use in relationship to quality measures in older patients with inflammatory bowel disease: a US Medicare cohort study. *BMJ Open* 2015;5(9):e008597. doi: 10.1136/bmjopen-2015-008597 [published Online First: 2015/09/09]
18. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43. doi: 10.1016/S0140-6736(12)60240-2 [published Online First: 2012/05/15]
19. Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analyses. *J Epidemiol Community Health* 2012;66(12):1177-81. doi: 10.1136/jech-2011-200168 [published Online First: 2012/04/12]
20. Argollo M, Gilardi D, Peyrin-Biroulet C, et al. Comorbidities in inflammatory bowel disease: a call for action. *Lancet Gastroenterol Hepatol* 2019 doi: 10.1016/S2468-1253(19)30173-6 [published Online First: 2019/06/07]
21. Cigolle CT, Langa KM, Kabeto MU, et al. Geriatric conditions and disability: the Health and Retirement Study. *Ann Intern Med* 2007;147(3):156-64. doi: 10.7326/0003-4819-147-3-200708070-00004 [published Online First: 2007/08/08]
22. Solomon D, Sue Brown A, Brummel-Smith K, et al. Best paper of the 1980s: National Institutes of Health Consensus Development Conference Statement: geriatric assessment methods for clinical decision-making. 1988. *J Am Geriatr Soc* 2003;51(10):1490-4. doi: 10.1046/j.1532-5415.2003.51471.x [published Online First: 2003/09/27]
23. Hamaker ME, Seynaeve C, Wymenga AN, et al. Baseline comprehensive geriatric assessment is associated with toxicity and survival in elderly metastatic breast cancer patients receiving single-agent chemotherapy: results from the OMEGA study of the Dutch breast cancer trialists' group. *Breast* 2014;23(1):81-7. doi: 10.1016/j.breast.2013.11.004 [published Online First: 2013/12/10]
24. Antonio M, Saldana J, Linares J, et al. Geriatric assessment may help decision-making in elderly patients with inoperable, locally advanced non-small-cell lung cancer. *Br J Cancer* 2018;118(5):639-47. doi: 10.1038/bjc.2017.455 [published Online First: 2018/01/31]
25. Puts MTE, Sattar S, Kulik M, et al. A randomized phase II trial of geriatric assessment and management for older cancer patients. *Support Care Cancer* 2018;26(1):109-17. doi: 10.1007/s00520-017-3820-7 [published Online First: 2017/07/26]
26. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet* 2013;381(9868):752-62. doi: 10.1016/S0140-6736(12)62167-9 [published Online First: 2013/02/12]
27. van Deudekom FJ, Schimberg AS, Kallenberg MH, et al. Functional and cognitive impairment, social environment, frailty and adverse health outcomes in older patients with head and neck cancer, a systematic review. *Oral Oncol* 2017;64:27-36. doi: 10.1016/j.oraloncology.2016.11.013 [published Online First: 2016/12/28]
28. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56(3):M146-56. doi: 10.1093/gerona/56.3.m146 [published Online First: 2001/03/17]