Göteborg, 2021

MECHANISMS UNDERLYING INFLAMMATION, SYMPTOMS AND QUALITY OF LIFE IN ULCERATIVE COLITIS

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, den 19 november 2021, klockan 12:30

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Avhandlingen baseras på följande delarbeten:

I. Mavroudis G, Simrén M, Jonefjäll B, Öhman L, Strid H. Symptoms compatible with functional bowel disorders are common in patients with quiescent ulcerative colitis and influence the quality of life but not the course of the disease. Therap Adv Gastroenterol. 2019;12:1756284819827689.

II. Mavroudis G, Magnusson MK, Isaksson S, Sundin J, Simrén M, Öhman L, Strid H. Mucosal and Systemic Immune Profiles Differ During Early and Late Phases of the Disease in Patients With Active Ulcerative Colitis. J Crohns Colitis. 2019;13(11):1450-8.

III. Mavroudis G, Strid H, Jonefjäll B, Simrén M. Visceral hypersensitivity is together with psychological distress and female gender associated with severity of IBS-like symptoms in quiescent ulcerative colitis. Neurogastroenterol Motil. 2021;33(3):e13998

IV. Mavroudis G, Simrén M, Öhman L, Strid H. Health-related quality of life in patients with longstanding ulcerative colitis in remission. Submitted.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

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Abstract

A substantial proportion of patients with ulcerative colitis (UC) in remission demonstrate gastrointestinal (GI) symptoms, despite the absence of ongoing inflammation in the colon. The underlying mechanisms of these symptoms are still not clear. Moreover, data concerning the cell types involved in the immunopathogenesis of UC are conflicting and this can be inherent to temporal variations in the immune responses during the disease course. The overall aim of this thesis was to characterize symptoms during UC remission to find underlying mechanisms and impact on health-related quality of life (HRQoL) and also to investigate temporal variations in immune responses during active disease.

In Paper I, 299 UC patients were included and 177 of those were followed up one year later. 18% of UC patients in remission had symptoms compatible with functional bowel disorders (FBD) other than IBS at enrollment. The total burden of GI symptoms in patients with symptoms compatible with FBD other than IBS in remission was higher than in patients without FBD, which had a negative impact on HRQoL. The presence of FBD-like symptoms was not correlated with psychological distress, systemic immune activity or subclinical colonic inflammation and was not a risk factor for active UC at follow-up one year later.

In Paper II, 15 patients with UC provided serum and mucosal biopsies during a flare in early (time of diagnosis) and late (after 10 years) disease to determine and compare systemic and mucosal immune profiles at these two time points. The profile of 15 serum proteins highly discriminated early and late disease and eight proteins were differently expressed at the two time points. The mRNA profiles in biopsies strongly discriminated early and late disease and 42 genes were differently expressed at early and late disease. Further, T helper (Th)1- and Th2-related genes were associated with early and late disease, respectively.

In Paper III, rectal sensitivity was assessed in 36 UC patients in remission, 18 with IBS-like symptoms and 18 without, with rectal balloon distensions. Moreover, their GI and psychological symptoms were evaluated. UC patients with IBS-like symptoms in remission had lower sensory thresholds and higher unpleasantness ratings than those without. The overall GI symptom severity, abdominal pain and bloating, but not diarrhea, constipation or satiety, were associated with rectal sensitivity. In multivariable analyses, rectal hypersensitivity, psychological distress and female gender were independently associated with GI symptom severity.

In Paper IV, 66 patients with inactive UC were included 10 years after the disease onset to determine HRQoL, and identify predictors thereof. HRQoL was measured with the Short Form Health Survey 36 (SF-36). The SF-36 domain scores were comparable to the general Swedish population, except for the Vitality domain, where UC patients scored lower. Gender, smoking, comorbidity and disease phenotype had no impact on HRQoL. In contrast, corticosteroid use and sick leave due to UC during the past year, persisting GI symptoms during remission and fatigue were independently associated with aspects of physical HRQoL. Only psychological distress contributed uniquely to poorer mental HRQoL.

Conclusions: The presence of GI symptoms in UC in remission is common and is associated with impaired HRQoL. Other determinants that negatively influence different aspects of HRQoL in inactive UC are preceding disease activity, fatigue and psychological distress. The pathogenesis of GI symptoms in quiescent UC is multifactorial and involves, among other factors, visceral hypersensitivity, psychological factors and female gender. Hence, these parameters should be taken into consideration in the management of patients with UC in remission. Finally, a transition from a Th1-predominant to a Th2-dominated immune response in the inflamed mucosa in UC is observed as the disease progresses from early to late stages, which can have future implications in providing individualized treatment of UC patients.

Keywords: ulcerative colitis, functional bowel disorders, irritable bowel syndrome, gut immunology, visceral hypersensitivity, health-related quality of life

ISBN: 978-91-8009-418-4 (Printed)
ISBN: 978-91-8009-419-1 (PDF)
http://hdl.handle.net/2077/68706