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Prediction model to safely cease anti-TNF therapy in Crohn's disease: individual patient data meta-analysis (IPD-MA)

R. W. M. Pauwels*[1], C. J. van der Woude[1], D. Nieboer[2], E. W. Steyerberg[2,3], M. J. Casanova[4], J. P. Gisbert[4], A. J. Lobo[5], C. W. Lees[6], N. A. Kennedy[5], T. Molnár[7], K. Szánto[7], E. Louis[8], J.-Y. Mary[9], M. Lukas[10,11], M. Duijvestein[12], S. Bots[12], G. R. A. M. D'Haens[12], A. C. de Vries[1]

[1]*Erasmus MC, Department of Gastroenterology and Hepatology, Rotterdam, The Netherlands,* [2]*Erasmus MC, Department of Public Health, Rotterdam, The Netherlands,* [3]*Leiden UMC, Department of Clinical Biostatistics and Medical Decision Making, Leiden, The Netherlands,* [4]*Madrid Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Department of Gastroenterology, Madrid, Spain,* [5]*Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Department of Gastroenterology and Hepatology, Sheffield, UK,* [6]*Western General Hospital, Department of Gastroenterology and Hepatology, Edinburgh, UK,* [7]*University of Szeged, Department of Medicine, Szeged, Hungary,* [8]*Centre Hospitalier Universitaire de Liège, Department of Gastroenterology and Hepatology, Liège, Belgium,* [9]*INSERM U717, Department of Biostatistics and Clinical Epidemiology, Paris, France,* [10]*IBD Clinical and Research Centre, Iscare a.s, Prague, Czech Republic,* [11]*Institute of Medical Biochemistry and Laboratory Diagnostics, 1st Medical Faculty and General Teaching Hospital, Prague, Czech Republic,* [12]*Amsterdam UMC, Academic Medical Centre, Department of Gastroenterology and Hepatology, Amsterdam, The Netherlands*

Background: Tools for patient stratification to safely cease anti-TNF therapy in Crohn's disease (CD) are urgently needed. This IPD-MA aims at development of a predictive diagnostic tool for a personalised approach towards anti-TNF cessation in CD.

Methods: A systematic literature search was conducted to identify studies investigating the risk of relapse and risk factors in CD patients after anti-TNF therapy cessation by using Medline Ovid, Embase, Cochrane, Web of Science and Google Scholar. Cohort studies with >50 CD patients in remission (clinical or biochemical or endoscopic/radiological) were selected. IPD from the original study databases were used for analysis. Inclusion criteria: luminal CD as indication for anti-TNF therapy, duration of treatment ≥6 months. We associated baseline demographic and clinical data (age, gender, smoking, disease duration, Montreal classification, history of surgical resection, type of anti-TNF medication, concomitant immunosuppressants, corticosteroids prior to cessation and previous anti-TNF therapy) with time to relapse using a Cox model. A prediction model was constructed following the 'TRIPOD' statement, with backward selection and $p > 0.2$ as selection criterion. To investigate the predictive performance internal-external validation was applied.

Results: A total of 10 cohort studies were identified, IPD were available from 6 studies. Anti-TNF was withdrawn in 1006 patients, who experienced 474 relapses after a median FU time of 14 months (IQR 8–28). At 1-year relapse rate was 36%, ranging from 24% to 44%. At 2-year relapse rate was 54% (41%-82%). Risk factors for relapse were age (HR 0.98, CI 0.97–0.99), smoking at baseline (HR 1.19 (CI 0.96–1.48), disease duration (HR 1.06, CI 1.03–1.10), disease location (L2) (HR 1.04, CI 0.77–1.41), disease location (L3) (HR 1.25, CI 0.96–1.62), +L4 (HR 1.50, CI 1.00–2.27), type of anti-TNF therapy (adalimumab vs. infliximab) (HR 1.18, CI 0.95–1.48), immunosuppressant use (HR 0.68, CI 0.54–0.85), steroid used 6–12 months prior to cessation (HR 1.24, CI 0.72–2.13), ≥1 anti-TNF therapy in medical history (HR 1.37, CI 1.04–1.80). The prediction model had a discriminative ability with a C-statistic of 0.62 (0.58–0.64). Biochemical parameters of remission (CRP, FC, haemoglobin, leucocytes), anti-TNF trough level and endoscopic data will be added to this preliminary prediction model.

Conclusions: The overall risk of relapse in CD patients in remission is 37% within 1 year after anti-TNF cessation. Despite associations between clinical parameters and relapse risk, individualised prediction solely based on clinical parameters remains challenging. Improvement of the discriminative ability of the prediction model may be anticipated after insertion of biochemical and endoscopic data.

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Advance of medical therapies may improve outcome of ulcerative colitis with cytomegalovirus infection

H. Kitamoto*, S. Yamamoto, M. Matsuura, Y. Honzawa, S. Yamada, M. Okabe, H. Seno

Graduate School of Medicine, Kyoto University, Department of Gastroenterology and Hepatology, Kyoto, Japan

Background: Cytomegalovirus (CMV) reactivation often makes ulcerative colitis (UC) refractory. Despite recent advance of medical treatment for UC, few studies evaluated whether change of UC management affected clinical course of UC with CMV infection.

Methods: A total of 140 CMV-IgG positive UC patients, who underwent colonoscopy with the polymerase chain reaction assay using colonic biopsy specimen (mucosal-PCR) to investigate CMV reactivation between October 2003 and December 2017, were enrolled in this retrospective observational study. We divided those patients into two cohorts, the early (October 2003–June 2009, $n = 44$) and the late period (July 2009–December 2017, $n = 96$), according to the timing of colonoscopy. We compared cumulative colectomy-free rate between two periods.

Results: There was no significant difference in baseline characteristics between two groups. The 5-year cumulative colectomy-free rate in the late period was higher than that in the early period (72.4% vs. 91.2%; $p < 0.05$, Figure 1). Of note, while approximately 70% of CMV seropositive patients had CMV reactivation in the early cohort, less than half patients did in the late cohort (68.2% vs. 42.7%; $p < 0.05$). Significantly less patients in the later period received corticosteroids at enrolment compared with those in the early period (40.9% vs. 22.9%; $p < 0.05$). Usage of other immunosuppressant including tacrolimus, TNF-α antagonist, and thiopurine at baseline was similar between two groups. The proportion of patients with initiation or dose escalation of corticosteroids after colonoscopy was significantly lower in the late period than in the early period (27.3% vs. 12.5%; $p < 0.05$). Tacrolimus was also administered after colonoscopy less frequently in the late period than in the early period (47.7% vs. 30.2%; $p < 0.05$). Furthermore, the 5-year cumulative colectomy-free rate of patients with CMV reactivation in the late period was higher than that in the early period (66.0% vs. 92.7%; $p < 0.05$, Figure 1), although anti-viral therapy was more frequently performed in the early period than the late period (80% vs. 22.0%; $p < 0.01$). The proportion of patients who received corticosteroids

after CMV reactivation were significantly lower in the late period (60% vs. 29.3%; $p < 0.01$).

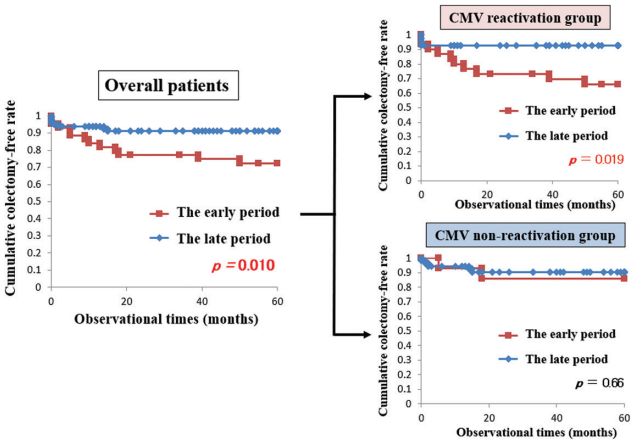

Figure 1. Cumulative colectomy-free rate.

Conclusions: Our results suggest that recent medical management for UC patients, especially optimisation of corticosteroid use, could not only decrease CMV reactivation, but avoid colectomy in patients with CMV reactivation, both of which results in improvement of the long-term outcome of UC patients with CMV seropositivity.

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Challenges in colonoscopic surveillance in chronic IBD

S.-L. Gillespie*[1], N. Singh-Clark[2], A. Shand[1], C. Lees[1], I. Arnott[1], G.-T. Ho[1], E. Watson[1], C. Noble[1], S. Din[1]
[1]*Edinburgh IBD Unit, Western General Hospital, Edinburgh, UK,* [2]*University of Edinburgh, Edinburgh, UK*

Background: Chronic inflammatory bowel disease (IBD) is associated with a 2- to 4-fold elevation of lifetime risk of colorectal cancer (CRC). Regular colonoscopic surveillance and the detection of colonic epithelial dysplasia are the gold standard for the early detection of CRC. Despite this, up to a third of patients will develop CRC within 3 years of a normal colonoscopy. We therefore aimed to calculate our post-colonoscopy CRC rate and identify the root causes for these cancers to inform where practice could be improved.

Methods: Surveillance colonoscopy procedures were extracted from Unisoft® from April 2008 to December 2015 to allow determination of the 3-year post colonoscopy cancer rate.

Results: 1460 procedures were undertaken including 845 males (58%) with a mean age of 53 years (range 17–88 years). The IBD diagnosis was: 1051 ulcerative colitis, 337 Crohn's disease and 72 IBD-Unclassified. Chromoendoscopy was adopted in 2012 and is achieved in approximately 50% of these procedures. Reasons for non-compliance with the use of chromoendoscopy include patient factors (poor bowel preparation, concurrent colonic inflammation and extensive pseudopolyposis), equipment factors (no dye spray) and endoscopist skill. Chromoendoscopy led to a significant reduction in the mean number of random colonic biopsies from 17 to 11 ($p < 0.05$). The post-colonoscopy cancer rate was <10% in our unit. Low-grade dysplasia was not a robust marker of future CRC compared with high-grade dysplasia.

Conclusions: We demonstrate the challenges in detecting CRC in patients with chronic IBD and confirm the poor clinical utility of low-grade dysplasia in predicting future CRC. There is an urgent need to develop more objective predictive biomarkers of future CRC risk.

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Faecal calprotectin correlates to UCEIS and can predict short-term recurrence in patients with ulcerative colitis

M. Naganuma*[1], T. Kobayashi[2], T. Kanai[1]
[1]*Division of Gastroenterology and Hepatology, Keio University, Tokyo, Japan,* [2]*Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, Tokyo, Japan*

Background: We recently reported that ulcerative colitis Index of Severity (UCEIS) of 0–1 is associated with better long-term prognosis while faecal calprotectin is a valuable biomarker for assessing the severity of UC. However, there have been only few large multi-centre cohort studies trying to predict short-term recurrences using faecal calprotectin (FCP).

Methods: The multi-centre prospective cohort study was conducted in 756 UC patients from 14 Japanese academic institutions. Median FCP level on each score of UCEIS (range 0–7) was calculated (Cohort 1) and the correlation between FCP and UCEIS was assessed using Kruskal–Wallis analysis. We also assessed the association of FCP level and clinical recurrence (partial Mayo score>2) in quiescent UC patients (partial Mayo score of 0–1) using the log-rank test and cox proportional hazard model(Cohort 2). A receiver-operating characteristic curve analysis was conducted to determine the cut-off value of the FCP at baseline for predicting mucosal healing and clinical recurrence. FC was measured by Fluoro Enzyme Immunoassay using EliA Calprotectin 2.

Results: The median FCP level increased gradually as UCEIS become higher ($p < 0.001$) although FCP level is difficult to distinct between UCEIS of 0 (IQR:18.8–143.8) and 1 (IQR: 32.9–222.8) or UCEIS of 2 (IQR: 39.8–862.0) and 3 (IQR: 81.4–858.3). Each UCEIS subscore (vessel, bleeding, and erosion/ulcers) strongly correlated to FCP level (all items; $p < 0.001$). A cut-off value of 131 mg/kg for FCP level had a sensitivity of 75% and a specificity of 71% to predict UCEIS of 0-1. In Cohort 2, 24 (6.3%) and 90 (23.7%) of 379 quiescent patients had recurrences within 3 and 12 months, respectively. A cut-off value of 156 mg/kg for FCP level had a sensitivity of 68% and a specificity of 82% to predict recurrence within 12 months. The recurrence rate in patients with FCP ≥ 156 mg/kg (55.4%) was significantly higher ($p < 0.001$) than those with FCP < 156 mg/kg (12.2%). In a multi-variate analysis, FCP ≥ 156 mg/kg was an independent risk for recurrence (HR 6.2; 95% CI 3.6–10.6). Regarding the recurrence within 3 months, a cut-off value of 263.5 mg/kg for FCP had a sensitivity of 56% and a specificity of 84% to predict recurrence. The recurrence rate within 3 months in patients with FCP ≥ 263.5 mg/g (31.6%) was significantly higher ($p < 0.001$) than those with FCP < 263.5 mg/kg (5.7%). Only 2 (1.4%) 144 patients with FCP < 30.6 mg/kg had recurrences within 3 months.

Conclusions: FCP levels are strongly correlated to UCEIS and appears to be predictors of both short- and middle-term of recurrence in quiescent UC patients.