

A prediction model for successful increase of adalimumab dose intervals in patients with Crohn's disease: secondary analysis of the pragmatic open-label randomised controlled non-inferiority LADI trial

Reinier C.A. van Linschoten, MD^{1,3,*}

Fenna M. Jansen, MD^{2*}

Renske W.M Pauwels, MD¹

Lisa J.T. Smits, MD PhD²

Femke Atsma, PhD⁴

Wietske Kievit, PhD⁵

Dirk J. de Jong, MD PhD²

Annemarie C. de Vries, MD PhD¹

Paul J. Boekema, MD PhD⁶

Rachel L. West, MD PhD³

Alexander G.L. Bodelier, MD PhD⁷

Ingrid A.M. Gisbertz, MD PhD⁸

Frank H.J. Wolfhagen, MD PhD⁹

Tessa E.H. Römken, MD PhD¹⁰

Maurice W.M.D. Lutgens, MD PhD¹¹

Adriaan A. van Bodegraven, MD PhD¹²

Prof Bas Oldenburg, MD PhD¹³

Prof Marieke J. Pierik, MD PhD¹⁴

Maurice G.V.M. Russel, MD PhD¹⁵

Nanne K. de Boer, MD PhD¹⁶

Rosalie C. Mallant-Hent, MD PhD¹⁷

Pieter C.J. ter Borg, MD PhD¹⁸

Andrea E. van der Meulen-de Jong, MD PhD¹⁹

Jeroen M. Jansen, MD²⁰

Sita V. Jansen, MD²¹

Adrianus C.I.T.L. Tan, MD PhD²²

Prof C. Janneke van der Woude, MD PhD^{1#}

Frank Hoentjen, MD PhD^{2,23 #}

on behalf of the LADI study group and the Dutch Initiative on Crohn and Colitis (ICC)

** Shared first authorship*

Shared last authorship

¹ *Erasmus MC, Department of Gastroenterology and Hepatology, Rotterdam, The Netherlands*

² *Radboud University Medical Center, Department of Gastroenterology and Hepatology, Nijmegen, The Netherlands*

³ *Franciscus Gasthuis & Vlietland, Department of Gastroenterology and Hepatology, Rotterdam, The Netherlands*

⁴ *Radboud University Medical Center, Radboud Institute for Health Sciences, Scientific Center for Quality of Healthcare, Nijmegen, The Netherlands*

⁵ *Radboud University Medical Center, Radboud institute for Health Science, Department for Health Evidence, Nijmegen, The Netherlands*

⁶ *Maxima Medical Center, Department of Gastroenterology and Hepatology, Eindhoven, The Netherlands*

⁷ *Amphia Hospital, Department of Gastroenterology and Hepatology, Breda, The Netherlands*

⁸ *Bernhoven Hospital, Department of Gastroenterology and Hepatology, Uden, The Netherlands*

⁹ *Albert Schweitzer Hospital, Department of Gastroenterology and Hepatology, Dordrecht, The Netherlands*

¹⁰ *Jeroen Bosch Hospital, Department of Gastroenterology and Hepatology, 's-Hertogenbosch, The Netherlands*

¹¹ *Elisabeth Twee Steden Ziekenhuis, Department of Gastroenterology and Hepatology, Tilburg, The Netherlands*

¹² *Zuyderland Medical Center, Department of Gastroenterology, Geriatrics, Internal and Intensive Care Medicine (Co-MIK), Sittard-Geleen/Heerlen, The Netherlands*

¹³ *UMC Utrecht, Department of Gastroenterology and Hepatology, Utrecht, The Netherlands*

¹⁴ *Maastricht University Medical Center +, Department of Gastroenterology and Hepatology, Maastricht, The Netherlands*

¹⁵ *Medisch Spectrum Twente, Department of Gastroenterology and Hepatology, Twente, The Netherlands*

¹⁶ *Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology Metabolism Research Institute, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands*

¹⁷ *Flevoziekenhuis, Department of Gastroenterology and Hepatology, Almere, The Netherlands*

¹⁸ *Ikazia Hospital, Department of Gastroenterology and Hepatology, Rotterdam, The Netherlands*

¹⁹ *Leiden University Medical Center, Department of Gastroenterology and Hepatology, Leiden, The Netherlands*

²⁰ *OLVG, Department of Gastroenterology and Hepatology, Amsterdam, The Netherlands*

²¹ *Reinier de Graaf Gasthuis,, Department of Gastroenterology and Hepatology, Delft, The Netherlands*

²² *CWZ Hospital, Department of Gastroenterology and Hepatology, Nijmegen, The Netherlands*

²³ *Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Canada*

CORRESPONDING AUTHOR

Frank Hoentjen, MD PhD

Associate Professor of Medicine

Division of Gastroenterology

2-20A Zeidler Ledcor Centre

8540 - 112 Street NW

University of Alberta

Edmonton, AB T6G 2P8

Tel: +1 780-492-8691

Fax: +1 780-492-8121

Email: hoentjen@ualberta.ca

SUPPLEMENTARY TABLES

Predictor	Successful dose interval increase 60.6% ¹	Failed dose interval increase 39.4% ¹
Smoking status		
<i>Current</i>	13%	19%
<i>Never or Ex</i>	87%	81%
Concomitant Immunosuppressants	18%	15%
Previous therapy with infliximab	44%	44%
Previous therapy with adalimumab	17%	13%
Disease duration (years)	12.4 (6.4, 18.2)	16.0 (7.8, 20.7)
Remission duration (years)	2.9 (1.3, 6.0)	2.4 (1.6, 5.7)
Time on adalimumab (years)	4.9 (2.2, 7.0)	5.0 (2.8, 7.0)
Previous IBD-related intra-abdominal surgeries	36%	48%
Age at diagnosis		
<i>A1 (<17)</i>	12%	17%
<i>A2 (17-40)</i>	78%	73%
<i>A3 (>40)</i>	10%	9.8%
Disease extent		
<i>L1, ileal</i>	25%	25%
<i>L2, colonic</i>	19%	23%
<i>L3, ileocolonic</i>	57%	53%
<i>L4, upper disease</i>	9.7%	20%
Disease phenotype		
<i>B1, non-stricturing, non-penetrating</i>	61%	55%
<i>B2, stricturing</i>	20%	32%
<i>B3, penetrating</i>	19%	13%
<i>P, perianal disease</i>	30%	29%
HBI	1.00 (0.00, 2.00)	2.00 (0.00, 4.00)
CRP (mg/L)	1.50 (1.00, 3.00)	1.30 (1.00, 3.80)
FCP (mg/kg)	24 (13, 56)	48 (18, 83)
Adalimumab level (µg/ml)	10.2 (8.1, 11.6)	9.1 (5.9, 11.9)

IBD: inflammatory bowel disease, HBI: Harvey-Bradshaw Index, FCP: faecal calprotectin, CRP: c-reactive protein

¹ Data are averaged over the imputed datasets, %; Median (IQR)

Supplementary Table 1: Baseline predictor values stratified by outcome

Supplementary 2. AUC, calibration intercept and calibration slope for the models predicting successful interval increase.

Estimate	Apparent	Optimism	Optimism-corrected
Minimal lambda			
AUC	0.73	0.09	0.63
Intercept	-0.41	-0.36	-0.05
Slope	1.92	0.81	1.11
One standard error rule			
AUC	0.70	0.07	0.63
Intercept	-0.93	-0.95	0.02
Slope	3.13	1.95	1.18
AUC: Area under the receiver operating characteristic curve, Intercept: Calibration intercept, Slope: Calibration slope			