

Anti-integrin antibody therapy in IBD

K.Shateri MD
Associate professor of gastroenterology
UMSU Spring 1404



Treatment summary of **moderate to severe** UC

INDUCTION OF REMISSION

- **Biologic agent**
  - **Anti-tumor necrosis factor (TNF) agent-based therapy**
    - Infliximab
    - Adalimumab
    - Golimumab
  - **Anti-integrin antibody**
    - Vedolizumab
  - **Anti-interleukin (IL) antibody-based therapy**
    - Ustekinumab
    - Mirikizumab
    - Risankizumab
    - Guselkumab
- **Sphingosine-1-phosphate (S1P) receptor modulators**
  - Ozanimod
  - Etrasimod
- **Glucocorticoids**

INDUCTION OF REMISSION

- Anti TNF:
  - Coexisting inflammatory disease such as rheumatoid arthritis, ankylosing spondylitis, or other conditions treated with anti-TNF therapy.
- Ustekinumab or mirikizumab:
  - Psoriasis or psoriatic arthritis.
- S1P receptor modulator:
  - Multiple sclerosis.
  - Other demyelinating condition.
- Vedolizumab or an anti-interleukin (IL):
  - Patients who are ≥65 years old.
  - History of recent infection (eg, pneumonia within the previous three months.

Nonresponders to initial therapy

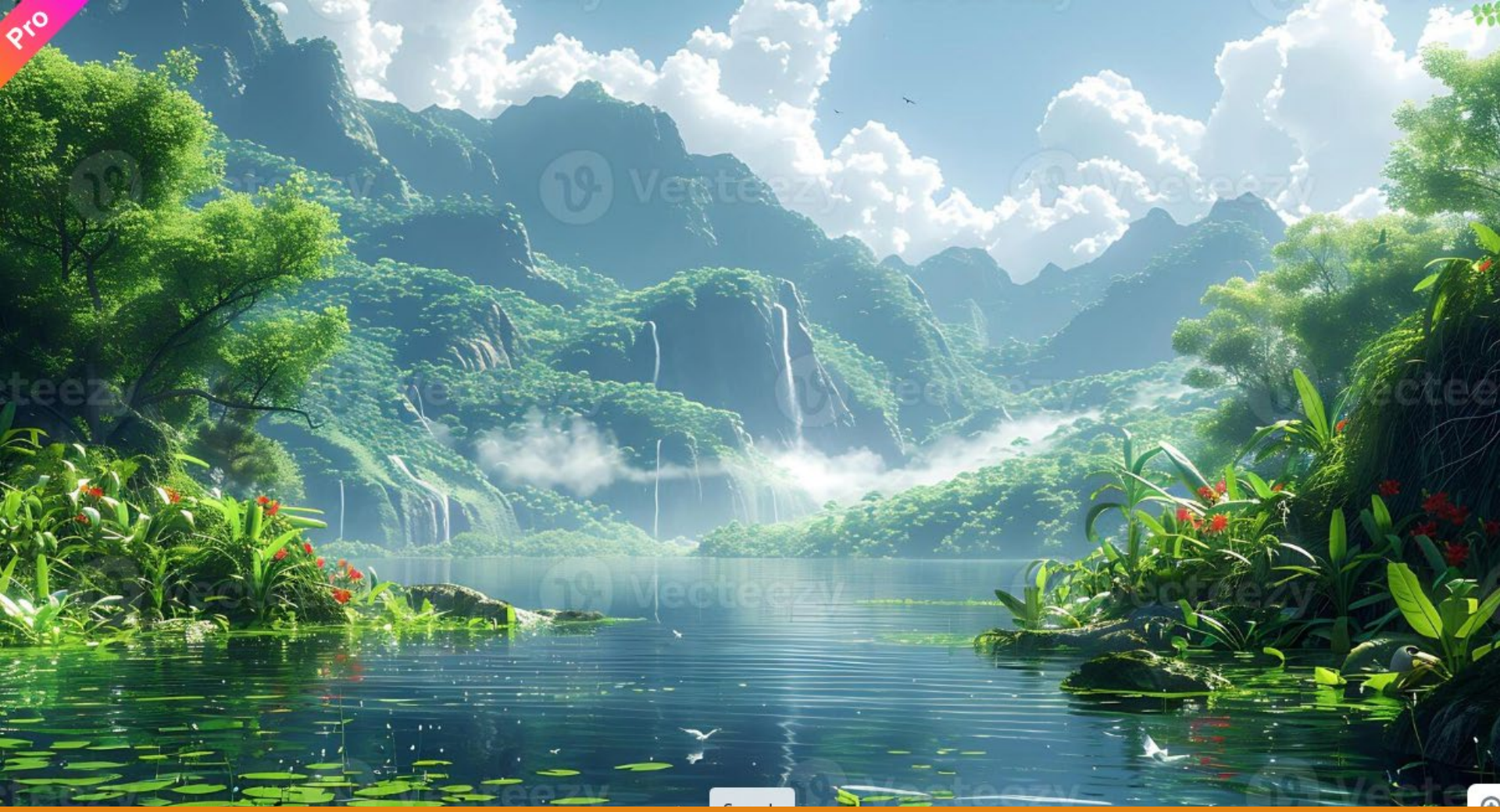
- For most patients who do not respond to initial biologic therapy and who have active inflammation (confirmed by endoscopy) in the absence of infection, we switch to:
  - An alternative agent from a different biologic class
  - A small molecule
    - **Janus kinase (JAK) inhibitors**
      - Tofacitinib Upadacitinib
    - **Sphingosine-1-phosphate (S1P) receptor modulators**
      - Ozanimod
      - Etrasimod
  - Intravenous glucocorticoids

Nonresponders to initial therapy

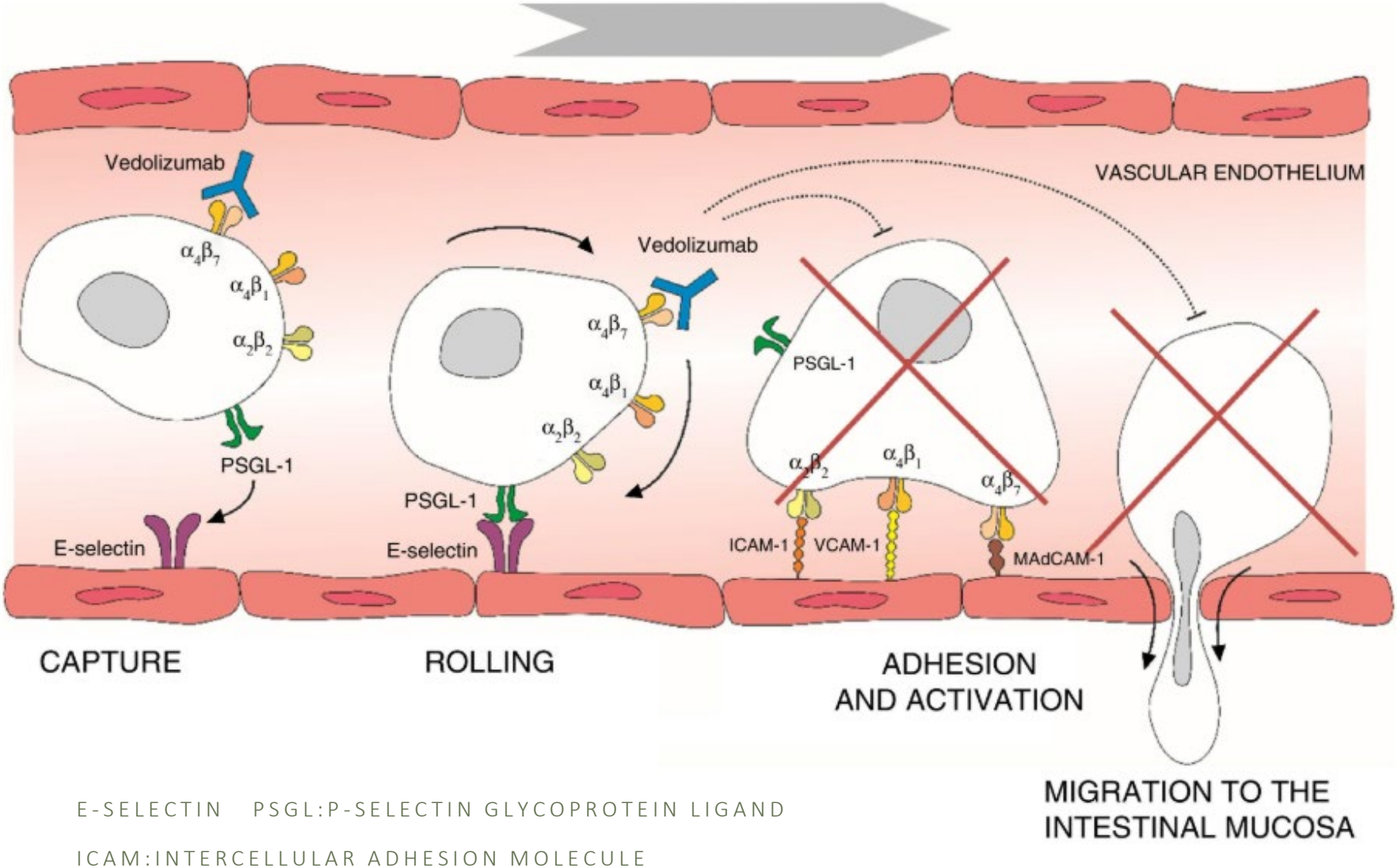
- For patients who do not respond to infliximab despite adequate drug levels:
  - Switch to a biologic agent from a different class
    - Anti-IL antibody-based therapy
    - Vedolizumab
  - Small molecule (eg, tofacitinib, upadacitinib, ozanimod, etrasimod)
  - Data from clinical trials in patients who did not respond or lost response to anti-TNF agents suggested that JAK inhibitors were effective as second-line therapy in such patients, whereas third-line options include vedolizumab or an oral S1P receptor modulator.

Nonresponders to initial therapy

- For patients who do not respond to injectable anti-TNF therapy monotherapy (eg, adalimumab, golimumab):
  - First try switching the injectable anti-TNF agent to infliximab infusion and adding azathioprine.
  - Switch to a biologic agent from a different class or a small molecule.
- For most patients who do not respond to initial biologic therapy with vedolizumab or anti-IL-based therapy:
  - Infliximab combined with an immunomodulator (eg, azathioprine).



Mecanism of action of vedolizumab

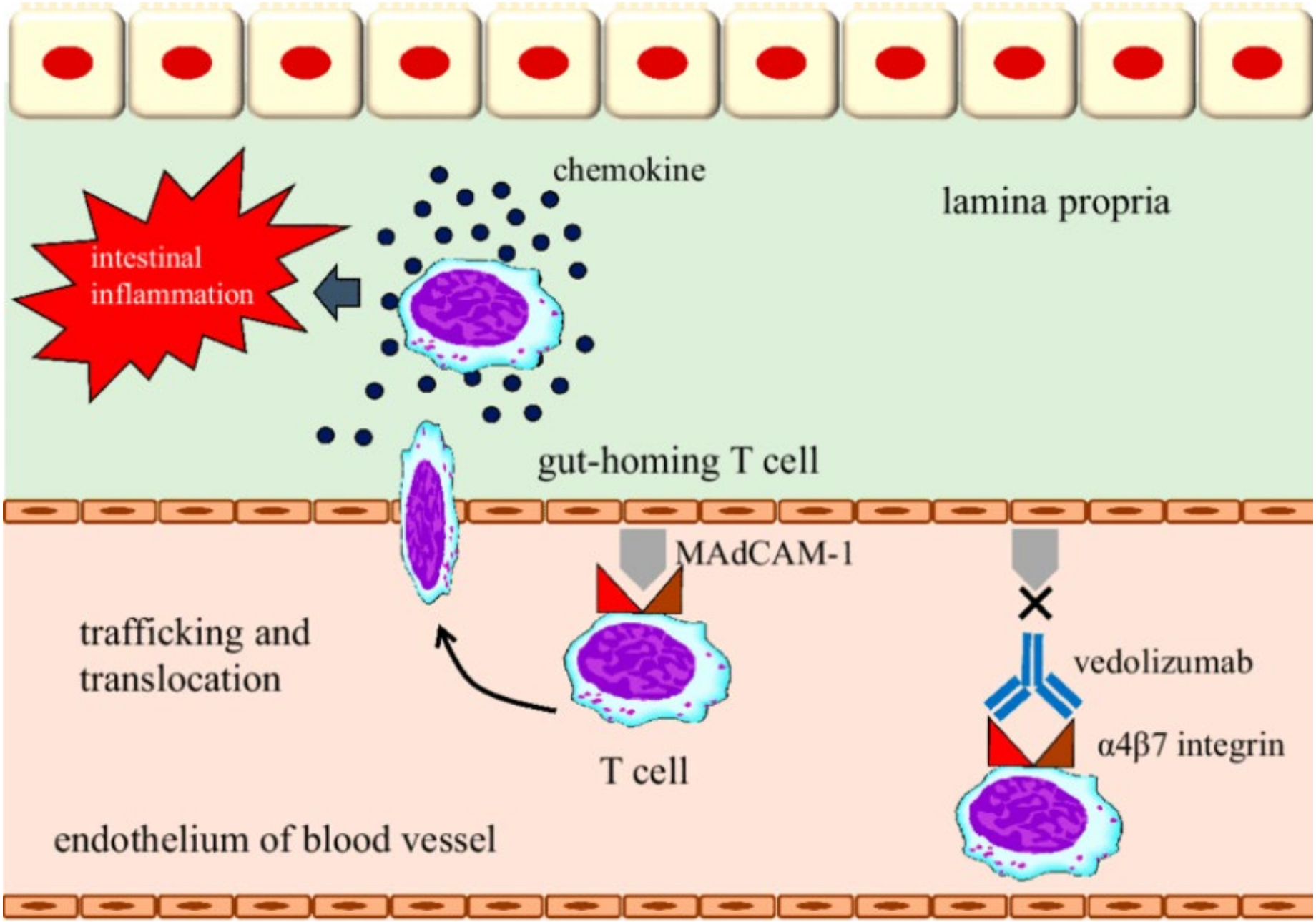


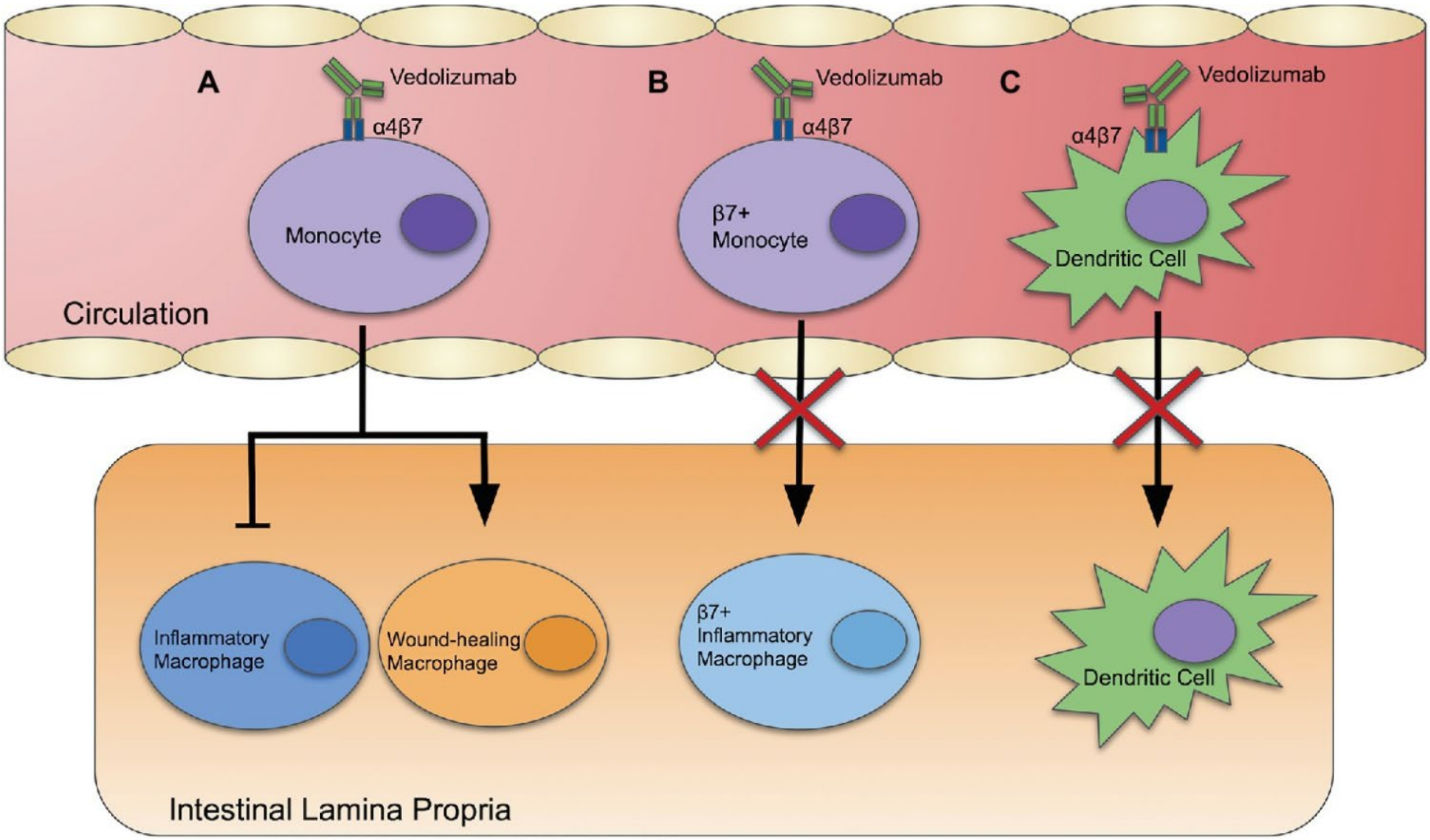
E-SELECTIN PSGL:P-SELECTIN GLYCOPROTEIN LIGAND

ICAM:INTERCELLULAR ADHESION MOLECULE

VCAM:VASCULAR CELL ADHESION MOLECULE

MADCAM:MUCOSAL ADDRESSIN CELL ADHESION MOLECULE


chemokine
lamina propria
intestinal inflammation
gut-homing T cell
MAdCAM-1
trafficking and translocation
vedolizumab
α4β7 integrin
T cell
endothelium of blood vessel


A
Vedolizumab
α4β7
Monocyte
B
Vedolizumab
α4β7
β7+
Monocyte
C
Vedolizumab
α4β7
Dendritic Cell
Circulation
Inflammatory
Macrophage
Wound-healing
Macrophage
β7+
Inflammatory
Macrophage
Dendritic Cell
Intestinal Lamina Propria

“Gut specific”- Targets lymphocyte trafficking to primarily luminal GI tract



This Is How I Understand Leukocyte Trafficking



Anti-integrin therapy

Leukocytes can't get to the bowel



S1P Receptor Modulators

Leukocytes can't get out of the garage



Vedolizumab in UC

The new england journal of medicine

2013 Aug 22

The NEW ENGLAND JOURNAL of MEDICINE

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Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis

Brian G. Feagan, M.D., Paul Rutgeerts, M.D., Ph.D., Bruce E. Sands, M.D., Stephen Hanauer, M.D., Jean-Frédéric Colombel, M.D., William J. Sandborn, M.D., Gert Van Assche, M.D., Ph.D., Jeffrey Axler, M.D., Hyo-Jong Kim, M.D., Ph.D., Silvio Danese, M.D., Ph.D., Irving Fox, M.D., Catherine Milch, M.D., Serap Sankoh, Ph.D., Tim Wyant, Ph.D., Jing Xu, Ph.D., and Asit Parikh, M.D., Ph.D., for the GEMINI 1 Study Group*

ABSTRACT

BACKGROUND

Gut-selective blockade of lymphocyte trafficking by vedolizumab may constitute effective treatment for ulcerative colitis.

METHODS

We conducted two integrated randomized, double-blind, placebo-controlled trials of vedolizumab in patients with active disease. In the trial of induction therapy, 374 patients (cohort 1) received vedolizumab (at a dose of 300 mg) or placebo intravenously at weeks 0 and 2, and 521 patients (cohort 2) received open-label vedolizumab at weeks 0 and 2, with disease evaluation at week 6. In the trial of maintenance therapy, patients in either cohort who had a response to vedolizumab at week 6 were randomly assigned to continue receiving vedolizumab every 8 or 4 weeks or to switch to placebo for up to 52 weeks. A response was defined as a reduction in the Mayo Clinic score (range, 0 to 12, with higher scores indicating more active disease) of at least 3 points and a decrease of at least 30% from baseline, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1.

From the Robarts Clinical Trials, Robarts Research Institute, and the Departments of Medicine and of Epidemiology and Biostatistics, University of Western Ontario, London, Canada (B.G.F.); Katholieke Universiteit and University Hospital Gasthuisberg, Leuven, Belgium (P.R., G.V.A.); Icahn School of Medicine at Mount Sinai, New York (B.E.S., J.-F.C.); University of Chicago, Chicago (S.H.); Département d'Hépato-gastroentérologie et Centre d'Investigations Cliniques, Centre Hospitalier Régionale Universitaire de Lille, Université Lille Nord de France, Lille, France (J.-F.C.); University of California, San Diego, La Jolla (W.J.S.); Toronto Digestive Disease Associates, University of Toronto, and Mount Sinai Hospital, Toronto (J.A.); Kyung Hee University Hospital, Seoul,

Vedolizumab as induction and maintenance therapy for ulcerative colitis

Vedolizumab was more effective than placebo as induction and maintenance therapy for ulcerative colitis

Coherence database of systematic review

2014 Aug 8



Vedolizumab for induction and maintenance of remission in ulcerative colitis (Review)

Bickston SJ, Behm BW, Tsoulis DJ, Cheng J, MacDonald JK, Khanna R, Feagan BG

Vedolizumab for induction and maintenance of remission in ulcerative colitis

- In a systematic review of three studies including over 600 patients with UC, patients given vedolizumab were less likely to fail to achieve clinical remission after six weeks of therapy compared with placebo (48 versus 72 percent, RR 0.68, 95% CI, 0.59 to 0.78)

Authors' conclusions

- Moderate to high quality data from four studies shows that vedolizumab is superior to placebo for induction of clinical remission and response and endoscopic remission in patients with moderate to severely active ulcerative colitis and prevention of relapse in patients with quiescent ulcerative colitis.
- Moderate quality data from one study suggests that vedolizumab is superior to placebo for prevention of relapse in patients with quiescent ulcerative colitis..

Authors' conclusions

- Adverse events appear to be similar to placebo.
- Future trials are needed to define the optimal dose, frequency of administration and long-term efficacy and safety of vedolizumab used for induction and maintenance therapy of ulcerative colitis.
- Vedolizumab should be compared to other currently approved therapies for ulcerative colitis in these trials

World J Gastrointest Pharmacol Therpeutics

2016 Feb 6

World Journal of Gastrointestinal Pharmacology and Therapeutics

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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MINIREVIEWS

Review of vedolizumab for the treatment of ulcerative colitis

Michelle SY Lau, Her Hsin Tsai

Michelle SY Lau, Her Hsin Tsai, IBD Unit, Gastroenterology Department, Castle Hill Hospital, HEY NHS Trust, Cottingham HU16 5JQ, United Kingdom

Author contributions: Lau MSY carried out all the literature searches and prepared the manuscript; Tsai HH made several revisions and prepared the manuscript for publication.

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therapy; Pharmacology; Safety and efficacy

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Core tip: Vedolizumab appears to be effective in the management of moderate to severe ulcerative colitis with a good safety profile.

Lau MSY, Tsai HH. Review of vedolizumab for the treatment of ulcerative colitis. *World J Gastrointest Pharmacol Ther* 2016; 7(1): 107-111 Available from: URL: http://www.wjgnet.com/2150-5349/full/v7/i1/107.htm DOI: http://dx.doi.org/10.4292/wjgpt.v7.i1.107

Review of vedolizumab for the treatment of ulcerative colitis

- Vedolizumab is a novel, humanised, monoclonal IgG1- type antibody, developed as a gut selective anti-integrin specifically targeting α4β7 integrins in the gut.
- Clinical studies have demonstrated efficacy in the induction and the maintenance of response and remission in UC.
- It does not appear to have the same safety issues as natalizumab with no reports of PML.

Review of vedolizumab for the treatment of ulcerative colitis

- Vedolizumab's role in the management algorithm of moderately to severe UC remains unclear.
- Further trials would be needed to answer several questions.
  - Firstly, should vedolizumab be used as the primary biologic after failure of conventional treatment?
  - Secondly, is vedolizumab effective in patients who are primary antiTNF failures?
  - Finally does it have a role in patients whohave had secondary loss of response to anti-TNFs?

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Long-term Efficacy of Vedolizumab for Ulcerative Colitis

- Patients with UC experienced clinical and HRQL improvements with continued vedolizumab treatment.
- Increased dosing frequency to every 4 weeks was beneficial in patients who had loss of response to 8-weekly dosing.

GUT

2017 May;66(5):839-851

OPEN ACCESS

ORIGINAL ARTICLE

The safety of vedolizumab for ulcerative colitis and Crohn's disease

Jean-Frédéric Colombel,[1] Bruce E Sands,[1] Paul Rutgeerts,[2] William Sandborn,[3] Silvio Danese,[4] Geert D'Haens,[5] Remo Panaccione,[6] Edward V Loftus Jr,[7] Serap Sankoh,[8] Irving Fox,[8] Asit Parikh,[8] Catherine Milch,[8] Brihad Abhyankar,[9] Brian G Feagan[10]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2015-311079).

For numbered affiliations see end of article.

Correspondence to
Professor Jean-Frédéric Colombel, Division of Gastroenterology, Inflammatory Bowel Disease Center, Icahn School of Medicine, Mount Sinai Hospital, 17 East 102nd Street, 5th Floor, New York, NY 10029, USA; jean-frederic.colombel@mssm.edu

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ABSTRACT

Objective Vedolizumab is a gut-selective antibody to $\alpha_4\beta_7$ integrin for the treatment of ulcerative colitis (UC) and Crohn's disease (CD). We report an integrated summary of the safety of vedolizumab.

Design Safety data (May 2009–June 2013) from six trials of vedolizumab were integrated. Adverse events were evaluated in patients who received ≥1 dose of vedolizumab or placebo and were reported as exposure-adjusted incidence rates as the number of patients experiencing the event per 100 person-years (PYs) of exposure. Predictors of serious infection were assessed using a Cox proportional hazards model.

Results In total, 2830 patients had 4811 PYs of vedolizumab exposure (median exposure range, 1–1977 days). No increased risk of any infection or serious infection was associated with vedolizumab exposure. Serious clostridial infections, sepsis and tuberculosis were reported infrequently (≤0.6% of patients). No cases of progressive multifocal leucoencephalopathy were observed. Independent risk factors for serious infection in UC were prior failure of a tumour necrosis factor α antagonist (HR, 1.99; 95% CIs 1.16 to 3.42; p=0.0122) and narcotic analgesic use (HR, 2.68; 95% CI 1.57 to 4.58; p=0.0003), and in CD were younger age (HR, 0.97; 95% CI 0.95 to 0.98; p<0.0001), corticosteroid (HR, 1.88; 95% CI 1.35 to 2.63; p=0.0002) or narcotic analgesic use (HR, 2.72; 95% CI 1.90 to 3.89;

Significance of this study

What is already known on this subject?

- Vedolizumab is a monoclonal antibody that targets the $\alpha_4\beta_7$ integrin and selectively prevents the infiltration of leucocytes into the gastrointestinal submucosa.
- The efficacy and safety of vedolizumab in adults with IBD have been demonstrated in several clinical trials with follow-up to 1 year.
- Safety issues such as progressive multifocal leucoencephalopathy, infection and malignancy have been associated with other therapeutic monoclonal antibodies that are used to treat UC and CD, such as tumour necrosis factor α antagonists and the integrin antagonist, natalizumab.

What are the new findings?

- Treatment with vedolizumab for up to 5 years in a population of over 2800 patients demonstrated a favourable safety profile.
- No cases of progressive multifocal leucoencephalopathy have been reported with vedolizumab to date.
- Vedolizumab is not associated with an

The safety of vedolizumab for ulcerative colitis and Crohn's disease

- Vedolizumab has a favourable safety profile with low incidence rates of serious infections, infusion-related reactions and malignancies over an extended treatment period.

The new england journal of medicine

2019 Sep 26

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis

Bruce E. Sands, M.D., Laurent Peyrin-Biroulet, M.D., Ph.D., Edward V. Loftus, Jr., M.D., Silvio Danese, M.D., Jean-Frédéric Colombel, M.D., Murat Törüner, M.D., Laimas Jonaitis, M.D., Ph.D., Brihad Abhyankar, F.R.C.S., Jingjing Chen, Ph.D., Raquel Rogers, M.D., Richard A. Lirio, M.D., Jeffrey D. Bornstein, M.D., and Stefan Schreiber, M.D., Ph.D., for the VARSITY Study Group*

ABSTRACT

BACKGROUND

Biologic therapies are widely used in patients with ulcerative colitis. Head-to-head trials of these therapies in patients with inflammatory bowel disease are lacking.

METHODS

In a phase 3b, double-blind, double-dummy, randomized, active-controlled trial conducted at 245 centers in 34 countries, we compared vedolizumab with adalimumab in adults with moderately to severely active ulcerative colitis to determine whether vedolizumab was superior. Previous exposure to a tumor necrosis factor inhibitor other than adalimumab was allowed in up to 25% of patients. The patients were assigned to receive intravenous infusions of 300 mg of vedolizumab on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (plus injections of placebo) or subcutaneous injections of 40 mg of adalimumab, with a total dose of 160 mg at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter until week 50 (plus infusions of placebo). Dose escalation was not permitted in either group. The primary outcome was clinical remission at week 52 (defined as a total score of ≤2 on the Mayo scale [range, 0 to 12, with higher scores indicating more severe disease] and no subscore >1 [range, 0 to 3] on any of the four Mayo scale components). To control for type I error, efficacy outcomes were analyzed with the use of a hierarchical testing procedure, with the variables in the following order: clinical remission, endoscopic improvement (subscore of 0 to 1 on the Mayo endoscopic component), and corticosteroid-free remission at week 52.

From the Icahn School of Medicine at Mount Sinai, New York (B.E.S., J.-F.C.); Nancy University Hospital, Nancy, France (L.P.-B.); Mayo Clinic College of Medicine, Rochester, MN (E.V.L.); Humanitas University, Milan (S.D.); Ankara University School of Medicine, Ankara, Turkey (M.T.); Lithuanian University of Health Sciences, Kaunas, Lithuania (L.J.); Takeda Development Centre Europe, London (B.A.); Takeda Development Center Americas, Cambridge, MA (J.C., R.R., R.A.L., J.D.B.); and the University Hospital Schleswig-Holstein, Kiel, Germany (S.S.). Address reprint requests to Dr. Sands at the Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Pl., Box 1069, New York, NY 10029, or at bruce.sands@mssm.edu; or to Dr. Schreiber at the Department of Medicine I, University Hospital Schleswig-Holstein, Rosalind-Franklin-Str. 12, Haus 5, 24105 Kiel, Germany, or at s.schreiber@mucosa.de.

Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis

- In a randomized trial including 769 patients with moderate to severe UC, patients assigned vedolizumab had higher rates of clinical remission (defined as total Mayo score ≤2 and no subscore >1) compared with patients assigned adalimumab (31 versus 22 percent; difference 9 percent, 95% CI 2-15) .
- However, rates of glucocorticoid-free clinical remission were lower in the vedolizumab group (13 versus 22 percent; difference -9 percent, 95% CI -18.9 to 0.4), although this was not statistically significant.
- Serious adverse events were numerically lower with vedolizumab (11 versus 14 percent), but rates of serious infections were similar (2 percent in each group).

Gastrenterology

2020 Feb



Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis

- Subcutaneous vedolizumab is effective as maintenance therapy in patients with moderately to severely active ulcerative colitis who had a clinical response to intravenous vedolizumab induction therapy. It has a favorable safety and tolerability profile.



Treatment summary of Moderate to severe Crohn's disease

Moderate to severe Crohn disease

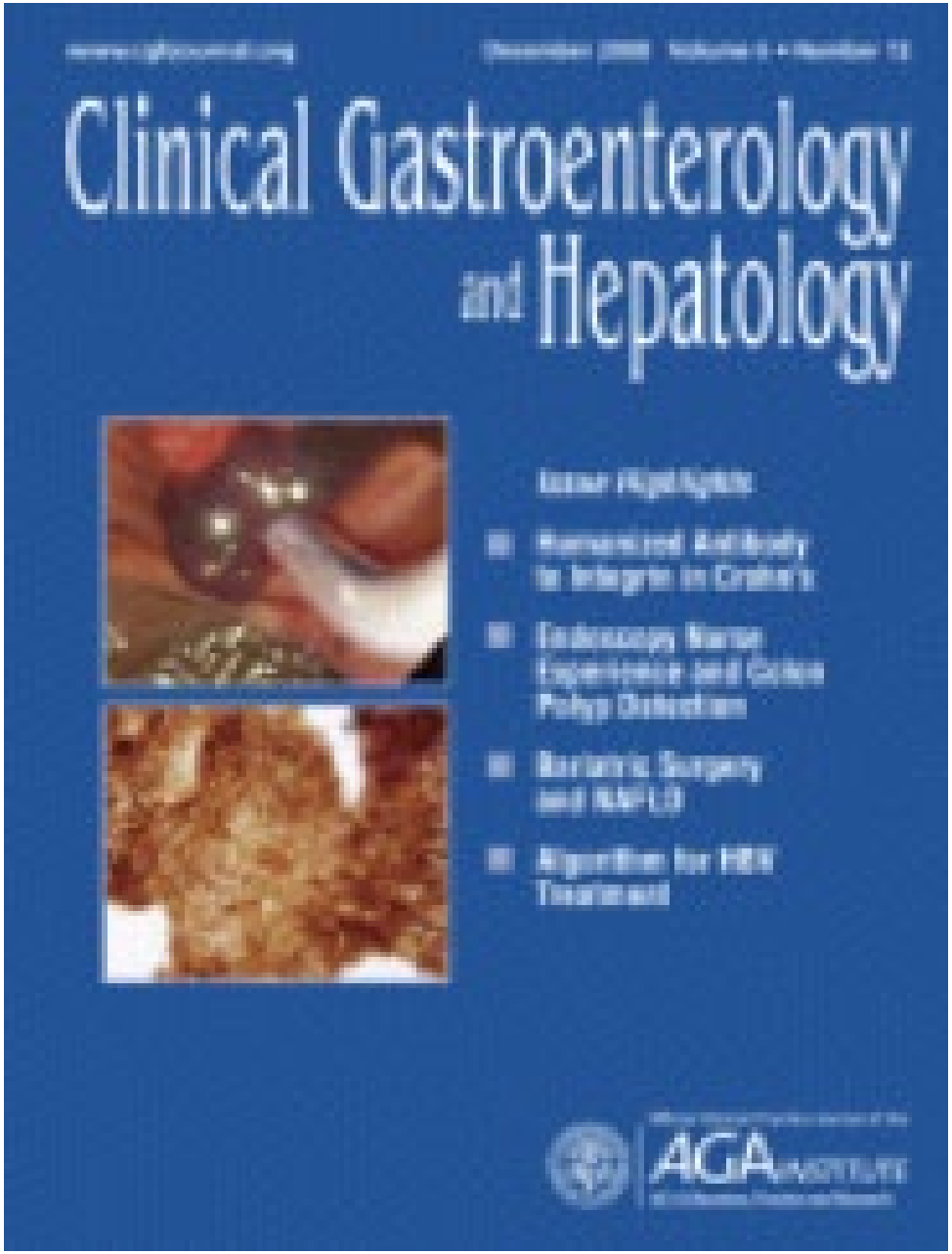
- For patients with moderate to severe Crohn disease who have fistulizing disease:
  - Combination therapy with an anti-TNF agent plus an immunomodulator (eg, azathioprine)
- For patients with moderate to severe Crohn disease and fistulizing complications in whom combination therapy (anti-TNF agent and immunomodulator) is not an option:
  - Anti-TNF monotherapy is an effective alternative
- For biologic naïve patients with moderate to severe Crohn disease without fistulizing complications, options for induction therapy include:
  - Anti-interleukin antibody monotherapy
  - Vedolizumab monotherapy
  - Anti-TNF therapy with or without an immunomodulator

Moderate to severe Crohn disease

- For patients who require second-line therapy (ie, nonresponders to initial biologic therapy and/or for patients who formed anti-drug antibodies to biologic agents),
  - Anti-interleukin antibody (eg, risankizumab, ustekinumab)
  - Vedolizumab may be used alone or in combination with an immunomodulator.
  - Upadacitinib

Clin Gastroenterol Hepatol.

December 2008



Clin Gastroenterol Hepatol

December 2008

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2008;6:1370–1377

Treatment of Active Crohn's Disease With MLN0002, a Humanized Antibody to the $\alpha 4\beta 7$ Integrin

BRIAN G. FEAGAN,* GORDON R. GREENBERG,‡ GARY WILD,§ RICHARD N. FEDORAK,‖ PIERRE PARÉ,¶ JOHN W. D. MCDONALD,# ALBERT COHEN,** ALAIN BITTON,§ JEFFREY BAKER,‡‡ RÉJEAN DUBÉ,§§ STEVEN B. LANDAU,‖‖ MARGARET K. VANDERVOORT,* and ASIT PARIKH¶¶

*Robarts Clinical Trials, Robarts Research Institute, London, Ontario, Canada; University of Western Ontario, London, Ontario, Canada; ‡Department of Medicine, Mt Sinai Hospital, University of Toronto, Toronto, Ontario, Canada; §Division of Gastroenterology, McGill University Healthcare Center, Montreal, Quebec, Canada; **Division of Gastroenterology, Department of Medicine, The Sir Mortimer B Davis Jewish General Hospital, McGill University, Montreal, Quebec, Canada; ‖Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; ¶Centre Hospitalier Affilié, Universitaire de Québec, Hôpital St-Sacrement, Quebec City, Quebec, Canada; #Department of Medicine, London Health Sciences Center–University Campus, University of Western Ontario, London, Ontario, Canada; ‡‡Division of Gastroenterology, St Michael's Hospital, Toronto, Ontario, Canada; §§L'Hôtel-Dieu de Québec, Quebec City, Quebec, Canada; ‖‖Healthcare Ventures, Cambridge, Massachusetts; and ¶¶Millennium Pharmaceuticals, Inc, Cambridge, Massachusetts

See Kappelman MD et al on page 1907 for companion article in the December 2008 issue of *Gastroenterology*.

Background & Aims: **Selective blockade of lymphocyte–vascular endothelium interactions in the gastrointestinal tract is a promising therapeutic strategy for inflammatory bowel disease. This randomized, double-blind, controlled trial assessed the efficacy and safety of MLN0002, a monoclonal antibody targeting the $\alpha 4\beta 7$ integrin, in patients with active Crohn's disease.** ***Methods:*** **Patients were randomized to receive MLN0002 2.0 mg/kg (n = 65), MLN0002 0.5 mg/kg (n = 62), or placebo (n = 58) by intravenous infusion on days 1 and 29. The primary efficacy end point was clinical response (≥70-point decrement in the Crohn's Disease Activity Index [CDAI] score) on day 57. Secondary end points were the proportions of patients with clinical remission (CDAI score ≤150) and with an enhanced clinical**

suppressives such as azathioprine, 6-mercaptopurine, and methotrexate.[2,3] The limitations of these therapies are substantial. Although effective for induction of remission, corticosteroids carry risks of both short- and long-term side effects, and are not effective for maintenance of remission.[4–6] The use of immunosuppressives is associated with infection,[7] an increased risk of lymphoma,[8,9] and bone marrow suppression.[3,10,11]

Antibodies directed against tumor necrosis factor-α, such as infliximab and adalimumab, represent a major advance in Crohn's disease therapy because they are effective for both induction and maintenance of remission.[12–15] However, the benefit of tumor necrosis factor-α antagonists is associated with serious infections including tuberculosis,[16] congestive heart failure, demyelinating disease, hypersensitivity, and, possibly, lymphoma.[17,18]

Pharmacologic interference with selective adhesion molecule interactions using humanized monoclonal antibodies is another promising treatment for inflammatory disorders.[19] Lymphocytes adhere to and migrate through vascular endothelium in response to inflammatory stimuli. Integrins are heterodimeric cell-surface

Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin

- This phase 2 study was suggestive of a dose-dependent beneficial effect of MLN0002 therapy on clinical remission.
- MLN0002 was well tolerated in patients with active Crohn's disease.

NEJM

2013 Aug 22;369(8)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease

William J. Sandborn, M.D., Brian G. Feagan, M.D., Paul Rutgeerts, M.D., Ph.D., Stephen Hanauer, M.D., Jean-Frédéric Colombel, M.D., Bruce E. Sands, M.D., Milan Lukas, M.D., Ph.D., Richard N. Fedorak, M.D., Scott Lee, M.D., Brian Bressler, M.D., Irving Fox, M.D., Maria Rosario, Ph.D., Serap Sankoh, Ph.D., Jing Xu, Ph.D., Kristin Stephens, B.A., Catherine Milch, M.D., and Asit Parikh, M.D., Ph.D., for the GEMINI 2 Study Group*

ABSTRACT

BACKGROUND

The efficacy of vedolizumab, an $\alpha_4\beta_7$ integrin antibody, in Crohn's disease is unknown.

METHODS

In an integrated study with separate induction and maintenance trials, we assessed intravenous vedolizumab therapy (300 mg) in adults with active Crohn's disease. In the induction trial, 368 patients were randomly assigned to receive vedolizumab or placebo at weeks 0 and 2 (cohort 1), and 747 patients received open-label vedolizumab at weeks 0 and 2 (cohort 2); disease status was assessed at week 6. In the maintenance trial, 461 patients who had had a response to vedolizumab were randomly assigned to receive placebo or vedolizumab every 8 or 4 weeks until week 52.

RESULTS

At week 6, a total of 14.5% of the patients in cohort 1 who received vedolizumab and 6.8% who received placebo were in clinical remission (i.e., had a score on the Crohn's Disease Activity Index [CDAI] of ≤150, with scores ranging from 0 to approximately 600 and higher scores indicating greater disease activity) (P=0.02); a total of 31.4% and 25.7% of the patients, respectively, had a CDAI-100 response (≥100-point decrease in the CDAI score) (P=0.23). Among patients in cohorts 1 and

From the University of California, San Diego, La Jolla (W.J.S.); Robarts Clinical Trials, Robarts Research Institute, and the Departments of Medicine and of Epidemiology and Biostatistics, University of Western Ontario, London (B.G.F.), University of Alberta, Edmonton (R.N.F.), and University of British Columbia, Vancouver (B.B.) — all in Canada; Katholieke Universiteit and University Hospital Gasthuisberg, Leuven, Belgium (P.R.); University of Chicago, Chicago (S.H.); Département d'Hépato-gastroentérologie et Centre d'Investigations Cliniques, Centre Hospitalier Régional Universitaire de Lille, Université Lille Nord de France, Lille, France (J.-F.C.); Icahn School of Medicine at Mount Sinai, New York (J.-F.C., B.E.S.); General Faculty Hospital, Prague, Czech Republic (M.L.); University of Washington, Seattle (S.L.); and Millennium Pharmaceuticals, Cambridge, MA (I.F., M.R., S.S., J.X., K.S., C.M., A.P.). Address reprint

Vedolizumab as induction and maintenance therapy for Crohn's disease

- Vedolizumab-treated patients with active Crohn's disease were more likely than patients receiving placebo to have a remission, but not a CDAI-100 response, at week 6; patients with a response to induction therapy who continued to receive vedolizumab (rather than switching to placebo) were more likely to be in remission at week 52.
- Adverse events were more common with vedolizumab.

Cochrane Database Syst Rev

2023 Jul 17

Cochrane Library

Cochrane Database of Systematic Reviews

Vedolizumab for induction and maintenance of remission in Crohn's disease (Review)

Hui S, Sinopoulou V, Gordon M, Aali G, Krishna A, Ding NS, Boyapati RK

Cochrane Database Syst Rev

2023 Jul 17

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Trusted evidence.
Informed decisions.
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[Intervention Review]

Vedolizumab for induction and maintenance of remission in Crohn's disease

Samuel Hui[1], Vassiliki Sinopoulou[2], Morris Gordon[2], Ghazaleh Aali[2,3], Anuj Krishna[4], Nik Sheng Ding[5], Ray K Boyapati[6]

[1]Department of Gastroenterology, Monash Medical Centre, Melbourne, Australia. [2]School of Medicine, University of Central Lancashire, Preston, UK. [3]Institute for Health Informatics Research, University College London, London, UK. [4]Austin Health, Melbourne, Australia. [5]Department of Gastroenterology, St Vincent's Hospital, Melbourne, Australia. [6]Department of Gastroenterology, Monash Medical Centre, Melbourne, Australia

Contact: Ray K Boyapati, ray.boyapati@monash.edu.

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Vedolizumab for induction and maintenance of remission in Crohn's disease

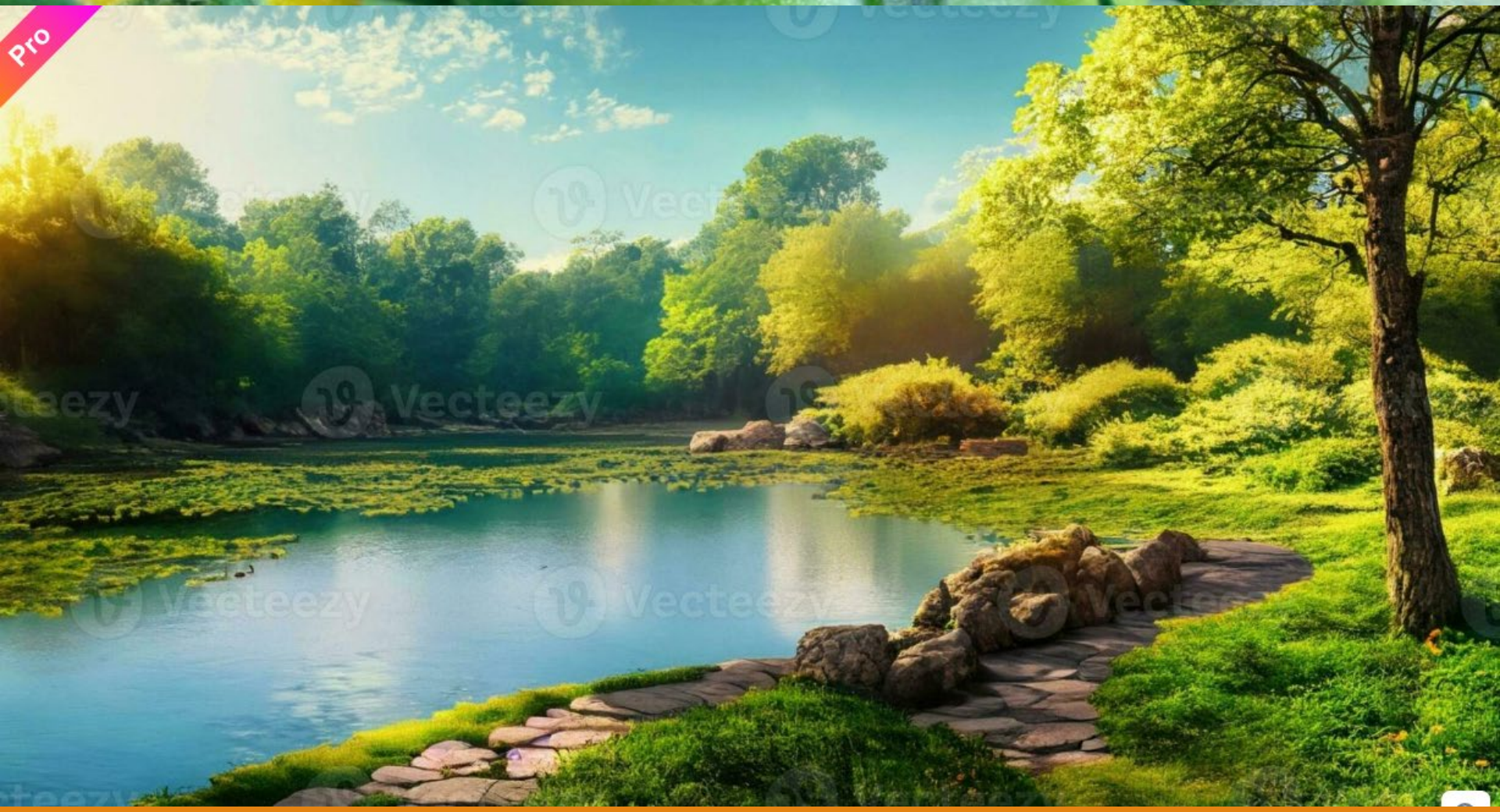
- High-certainty data across four induction and three maintenance trials demonstrate that vedolizumab is superior to placebo in the induction and maintenance of remission in Crohn's disease.
- Overall adverse events are probably similar and serious adverse events may be similar between vedolizumab and placebo during both induction and maintenance phases of treatment.
- Head-to-head research comparing the efficacy and safety of vedolizumab to other biological therapies is required.

Vedolizumab for induction and maintenance of remission in Crohn's disease

- Vedolizumab is often used as first-line therapy for patients over the age of 60 years or for those who have a history of malignancy or infectious complications .
- Vedolizumab can be used with or without an immunomodulator for patients with active moderate to severe Crohn disease .
- For first-line biologic therapy, we use vedolizumab as monotherapy, but if used as a second- or third-line agent and/or the patient has a history of antidrug antibodies to monoclonal agents, we may use vedolizumab in combination with an immunomodulator.
- However, due to the low immunogenicity rates of vedolizumab, we more frequently use it as a monotherapy agent.

Vedolizumab for induction and maintenance of remission in Crohn's disease

- In a meta-analysis of four induction trials including 1126 patients with Crohn disease, vedolizumab resulted in higher rates of clinical remission at 6 to 10 weeks compared with placebo (19.8 versus 11.6 percent, RR 1.61, 95% CI 1.2-2.17) .
- In a meta-analysis of three maintenance trials including 894 patients with Crohn disease, vedolizumab resulted in higher rates of sustained clinical remission after 52 to 60 weeks compared with placebo (42.5 versus 27.1 percent, RR 1.52, 95% CI 1.24-1.87).
- In addition, the rates of overall adverse events were not significantly different between the treatment and placebo groups.



vaccination

vaccination

- Hepatitis B surface antigen (HbsAg), hepatitis B surface antibody, and hepatitis B core antibody (anti-HBc).
- Hepatitis C virus (HCV) antibody. However, chronic HCV infection is not a contraindication for immunosuppressive therapy.
- Interferon-gamma release assay such as QuantiFERON-TB Gold In-Tube assay (preferred) or tuberculin skin test.
  - If the screening test for latent tuberculosis is indeterminate or positive, a chest radiograph is obtained, and the patient is referred to an infectious disease specialist for further evaluation.

vaccination

- Documenting immunity to varicella (eg, varicella zoster virus [VZV] IgG, clinician diagnosis of disease).
  - For patients with evidence of immunity who are ≥19 years old, we assess the need for and timing of zoster (shingles) vaccination.
  - For patients without evidence of immunity, we assess the need for VZV vaccination based on patient age and risk status.
- Serologic testing for Epstein-Barr virus (EBV) and cytomegalovirus (CMV).
  - We obtain anti-EBV and anti-CMV antibodies to assess for evidence of prior infection and thus the patient's risk of reactivation .



Dosage guidance

Ulcerative colitis

- **IV:** 300 mg at 0, 2, and 6 weeks and then every 8 weeks thereafter. Discontinue therapy in patients who show no evidence of therapeutic benefit by week 14.
- **SUBQ:**
  - Maintenance: 108 mg once every 2 weeks beginning after at least 2 IV infusions; administer in place of next scheduled IV dose and then every 2 weeks thereafter.
  - *Missed dose:* Administer next dose as soon as possible and then every 2 weeks thereafter.

Crohn disease:

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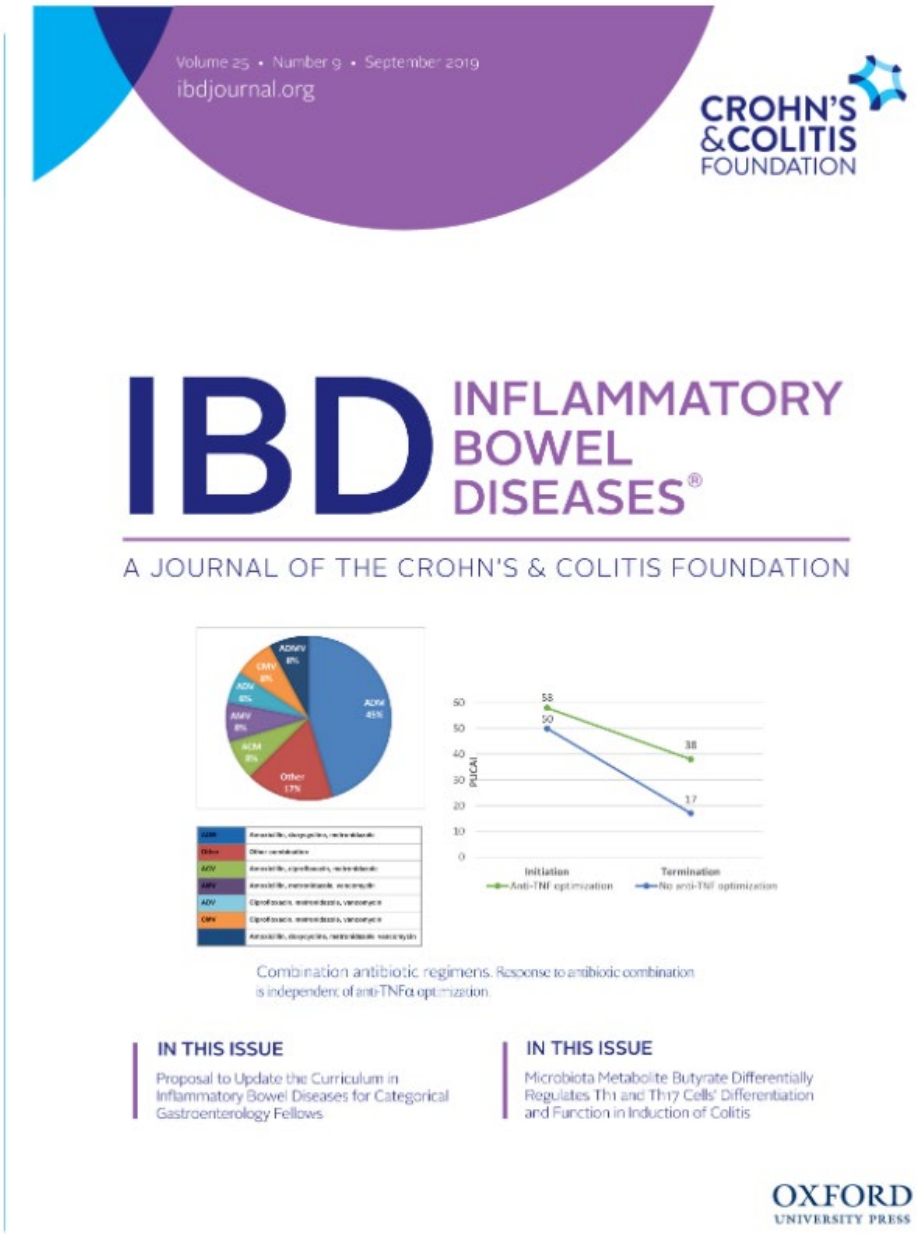
Pouchitus

Inflamm Bowel Dis

Volume 25, Number 9, September 2019

Cover image



Inflamm Bowel Dis

Volume 25, Number 9, September 2019

ORIGINAL RESEARCH ARTICLE—CLINICAL

Efficacy of Vedolizumab for Refractory Pouchitis of the Ileo-anal Pouch: Results From a Multicenter US Cohort

Martin Gregory, MD,[*] Kimberly N. Weaver, MD,[†] Patrick Hoversten, MD,[‡] Stephen Bradley Hicks, MD,[‡] Devin Patel, MD,[§] Matthew A. Ciorba, MD,[,¶] Alexandra M. Gutierrez, MD,[*,¶] Poonam Beniwal-Patel, MD,[††] Sowmya Palam, MD,[‡‡] Gaurav Syal, MD,[§§] Hans H. Herfarth, MD, PhD,[†,‖,**] George Christophi, MD, PhD,[*,¶] Laura Raffals, MD,[***] Edward L. Barnes, MD, MPH,[†,‖] and Parakkal Deepak, MBBS, MS[*,¶]*

Background and Aims: Inflammation of the pouch after ileal pouch-anal anastomosis (IPAA) can significantly impact quality of life and be difficult to treat. We assessed the effectiveness and safety of vedolizumab in Crohn's disease (CD) of the pouch and chronic antibiotic-dependent or antibiotic-refractory pouchitis.

Methods: This was a retrospective, multicenter cohort study at 5 academic referral centers in the United States. Adult patients with endoscopic inflammation of the pouch who received vedolizumab were included. The primary outcome was clinical response at any time point. Secondary outcomes included clinical remission, endoscopic response, and remission. Univariate analysis and multivariate analysis were performed for the effect of the following variables on clinical response: fistula, onset of pouchitis less than 1 year after IPAA, younger than 35 years old, gender, previous tumor necrosis factor inhibitor-alpha use, and BMI >30.

Results: Eighty-three patients were treated with vedolizumab for inflammation of the pouch between January 2014 and October 2017. Median follow-up was 1.3 years (interquartile range 0.7–2.1). The proportion of patients that achieved at least a clinical response was 71.1%, with 19.3% achieving clinical remission. Of the 74 patients with a follow-up pouchoscopy, the proportion of patients with endoscopic response and mucosal healing was 54.1% and 17.6%, respectively. Patients who developed pouchitis symptoms less than 1 year after undergoing IPAA were less likely to respond to vedolizumab, even after controlling for other risk factors.

Conclusions: Vedolizumab is safe and effective in the management of CD of the pouch and chronic pouchitis. Further studies are needed to compare vedolizumab with other biologic therapies for pouchitis and CD of the pouch.

Key Words: pouchitis, vedolizumab, Crohn's disease

Efficacy of Vedolizumab for Refractory Pouchitis of the Ileo-anal Pouch: Results From a Multicenter US Cohort

- In a systematic review of seven studies including 44 patients with chronic pouchitis who were treated with vedolizumab, 33 patients (75 percent) had symptomatic improvement at 12 weeks, and 28 of 38 patients (74 percent) had endoscopic improvement at six months .
- In a randomized trial including 102 patients with active chronic pouchitis, vedolizumab resulted in higher rates of combined clinical and endoscopic remission as measured by the modified PDAI compared to placebo after 14 weeks (31 versus 10 percent) .
- Vedolizumab also resulted in higher rates of sustained remission after 34 weeks (35 versus 18 percent).
- Rates of serious adverse events were numerically similar between groups.

NEJM

March 30, 2023

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vedolizumab for the Treatment of Chronic Pouchitis

S. Travis, M.S. Silverberg, S. Danese, P. Gionchetti, M. Löwenberg, V. Jairath, B.G. Feagan, B. Bressler, M. Ferrante, A. Hart, D. Lindner, A. Escher, S. Jones, and B. Shen, for the EARNEST Study Group*

ABSTRACT

BACKGROUND

Approximately half the patients with ulcerative colitis who undergo restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) will subsequently have pouchitis, and among those patients, one fifth will have chronic pouchitis.

METHODS

We conducted a phase 4, double-blind, randomized trial to evaluate vedolizumab in adult patients in whom chronic pouchitis had developed after undergoing IPAA for ulcerative colitis. Patients were assigned (in a 1:1 ratio) to receive vedolizumab intravenously at a dose of 300 mg or placebo on day 1 and at weeks 2, 6, 14, 22, and 30. All the patients received concomitant ciprofloxacin from weeks 1 to 4. The primary end point was modified Pouchitis Disease Activity Index (mPDAI)–defined remission (an mPDAI score of ≤4 and a reduction from baseline of ≥2 points in the mPDAI total score; scores range from 0 to 12, with higher scores indicating more severe pouchitis) at week 14. The mPDAI is based on clinical symptoms and endoscopic findings. Other efficacy end points included mPDAI-defined remission at week 34, mPDAI-defined response (a reduction from baseline of ≥2 points in the mPDAI score) at weeks 14 and 34, and PDAI-defined remission (a PDAI score of ≤6 and a reduction from baseline of ≥3 points; scores range from 0 to 18, with higher scores indicating more severe pouchitis) at weeks 14 and 34. The PDAI is based on clinical symptoms, endoscopic findings, and histologic findings

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Travis can be contacted at simon.travis@kennedy.ox.ac.uk or at the Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom.

*A complete list of investigators in the EARNEST Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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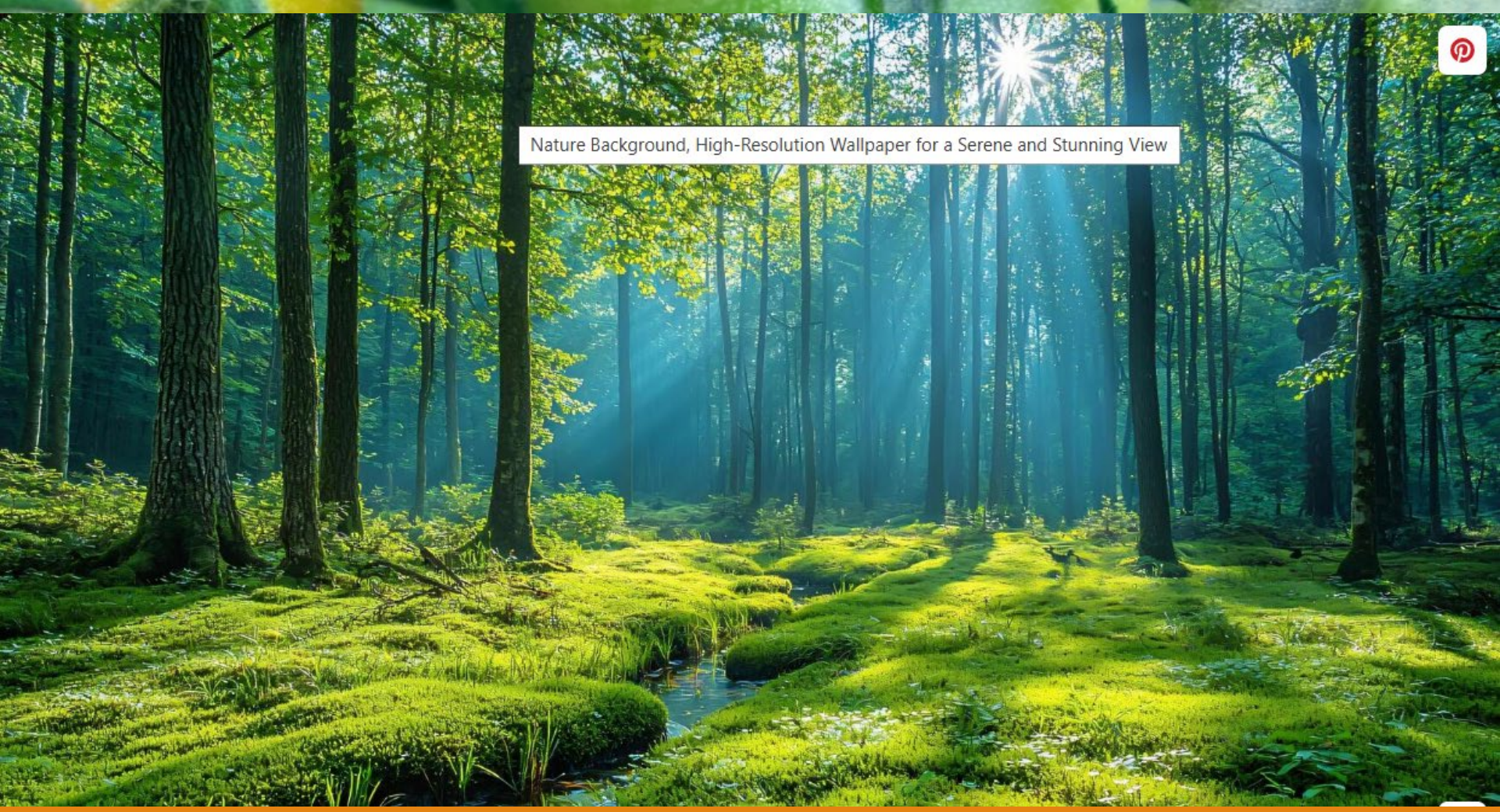
CME at NEJM.org

Vedolizumab for the Treatment of Chronic Pouchitis

- Treatment with vedolizumab was more effective than placebo in inducing remission in patients who had chronic pouchitis after undergoing IPAA for ulcerative colitis.



Adverse Reactions (Significant)



Infusion-related hypersensitivity and/or cutaneous reactions

Infusion-related hypersensitivity and/or cutaneous reactions

- Infusion-related reactions have been reported, including symptoms resembling anaphylaxis.
- Symptoms include
  - Flushing
  - Skin rash
  - Urticaria
  - Arthralgia
  - Myalgias
  - Fever
- Acute noncardiac chest pain has also been reported

Infusion-related hypersensitivity and/or cutaneous reactions

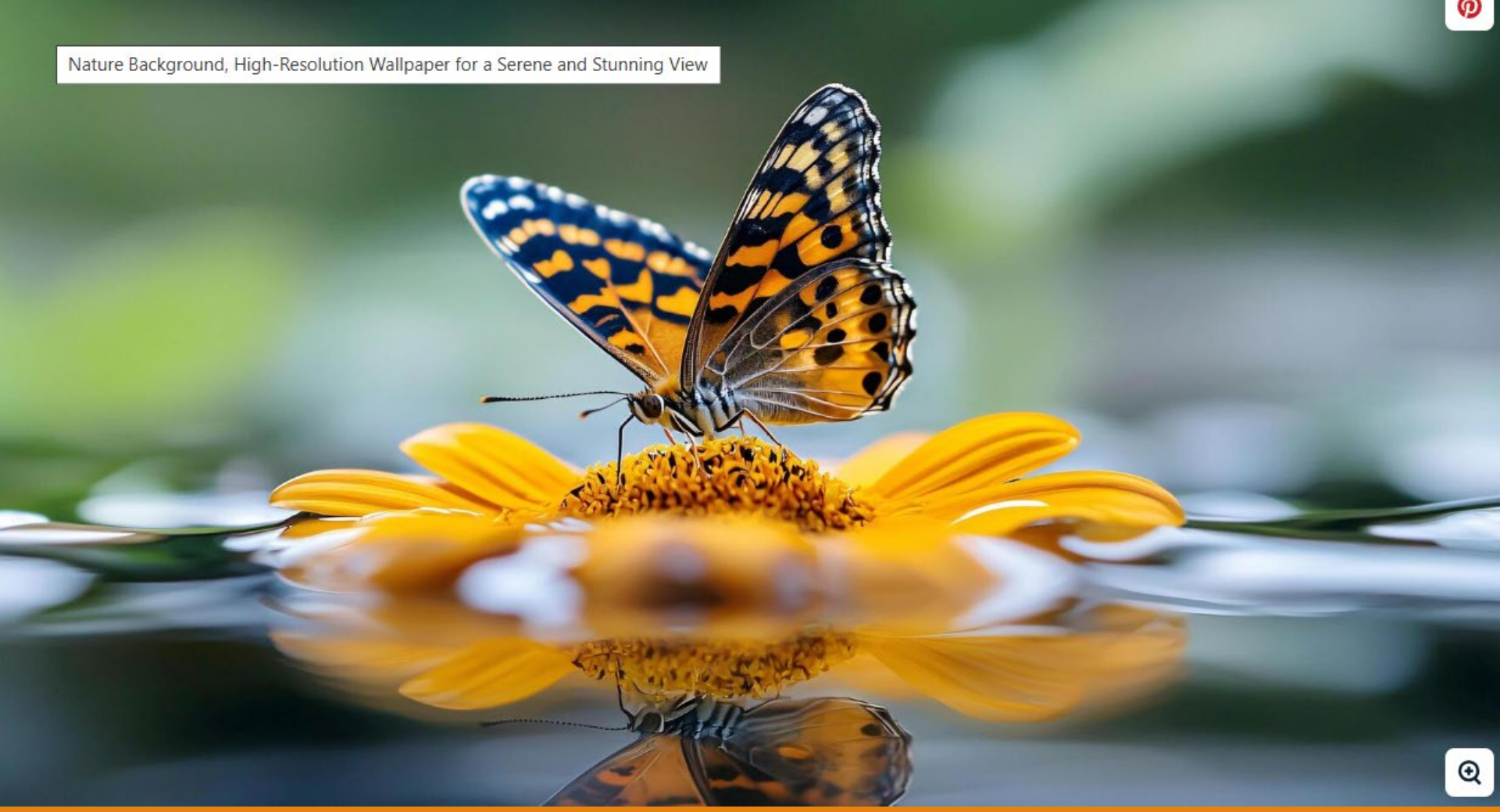
- Other cutaneous manifestations
  - IgA-mediated leukocytoclastic vasculitis
  - Henoch-Schönlein purpura
  - Nodular vasculitis,
  - Pyoderma gangrenosum)
- Have been reported and may be delayed, occurring weeks to months after initiation therapy .

Mechanism

- *Immediate:*
  - Vedolizumab also contains polysorbate 80, which is a known excipient that can induce immediate hypersensitivity reactions .
- *Delayed reactions:*
  - Unknown; dermatological-associated events may be triggered by the impact of vedolizumab on peripheral skin inflammatory cascades.
  - Other infusion-related reactions may result from development of anti-vedolizumab antibodies, which have been detected in severe reactions including noncardiac chest pain during the infusion.

Onset

- Varied; most infusion-related reactions have occurred within 2 hours of the completion of the infusion but can occur within minutes of the start of the infusion .
- In general, cutaneous vasculitis and other cutaneous reactions typically occur within 7 to 10 days of the inducing factor but have been identified after several vedolizumab infusions were previously tolerated and can occur after weeks or month.



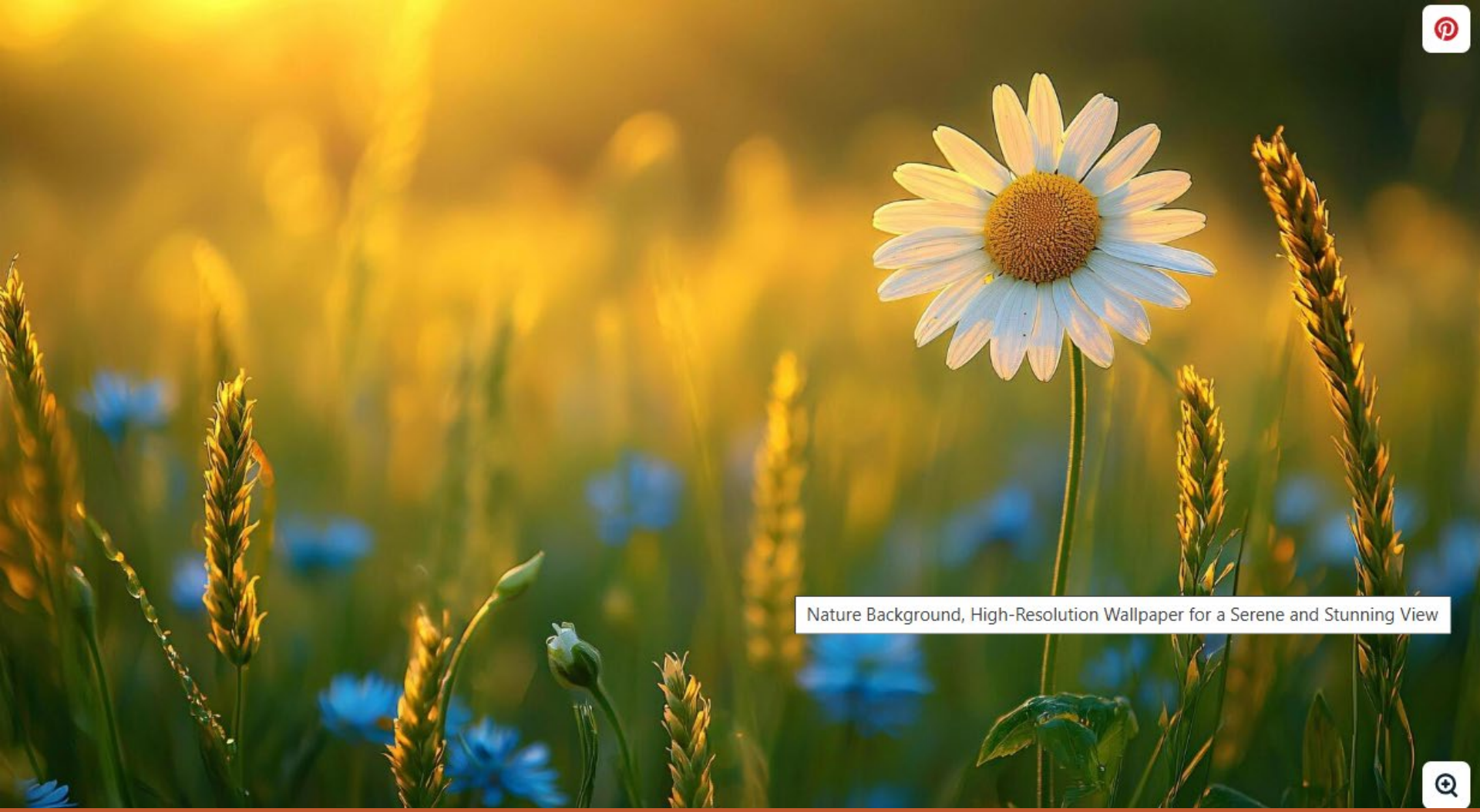
Hepatic injury

Hepatic injury

- Increased serum alanine aminotransferase and increased serum aspartate aminotransferase (≥3 times the upper limit of normal) have been reported with vedolizumab .
- Increased serum transaminases are commonly encountered in patients with inflammatory bowel disease , while the incidence of vedolizumab-induced hepatic injury is rare .
- Reported cases of vedolizumab-induced hepatic injury may present as mixed or cholestatic, and liver biochemistries tend to improve upon discontinuation .
- Underlying liver diseases (eg, primary biliary sclerosis) must also be excluded if vedolizumab-induced hepatic injury is suspected .

Hepatic injury

- *Mechanism:* Not clearly established; vedolizumab inhibits α4β7 integrin, selectively preventing gut specific signaling of T-lymphocytes and eosinophil migration and adhesion, which may increase peripheral eosinophilia commonly seen in allergic reactions such as immune-mediated hepatic injury .
- *Onset:* Varied; range reported is 14 to 275 days after exposure .
- *Risk factors:*
  - Previous injury
  - Current alcohol use
  - Older age ≥55 years



Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy

- Progressive multifocal leukoencephalopathy (PML) is a neurological disorder characterized by severe disability that can be fatal and is caused by John Cunningham virus (JCV) in the setting of significant immunosuppression .
- Natalizumab has been linked to an increased risk of PML and has a similar mechanism of action to vedolizumab, therefore prompting concerns for evaluation and monitoring of PML in patients receiving therapy.
- Unlike natalizumab, vedolizumab targets a different subunit of integrin expressed on gut-homing T-lymphocytes and does not impact immune surveillance within the central nervous system .
- Cases of vedolizumab-associated PML have yet to be identified, and the risk remains theoretical and based on data from natalizumab exposure .

Progressive multifocal leukoencephalopathy

- *Mechanism:* Time related (delayed); related to the pharmacologic action (ie, monoclonal antibody targeting α4β7 integrin, a cell surface glycoprotein on B and T lymphocytes that binds to mucosal addressin cell adhesion molecule-1 on the intestinal vasculature) .
- *Onset:* Delayed; occurs after 30 days of drug therapy (based on data from natalizumab).
- *Risk factors:*
  - Duration of therapy >2 years
  - Prior or concurrent immunosuppression during therapy
  - Positive JCV antibody identified prior to or during therapy
  - History of blood cancers



Serious infections

Serious infections

- Although the immunosuppressive activity of vedolizumab is focused on gut specific pathways, use may be associated with an increased risk for developing infection; most reported infections included upper respiratory tract infections and nasopharyngitis.
- The risk of serious infections, requiring hospitalization, is like other anti-TNF agents based on recent pooled analyses and have resolved with treatment discontinuation .

Serious infections

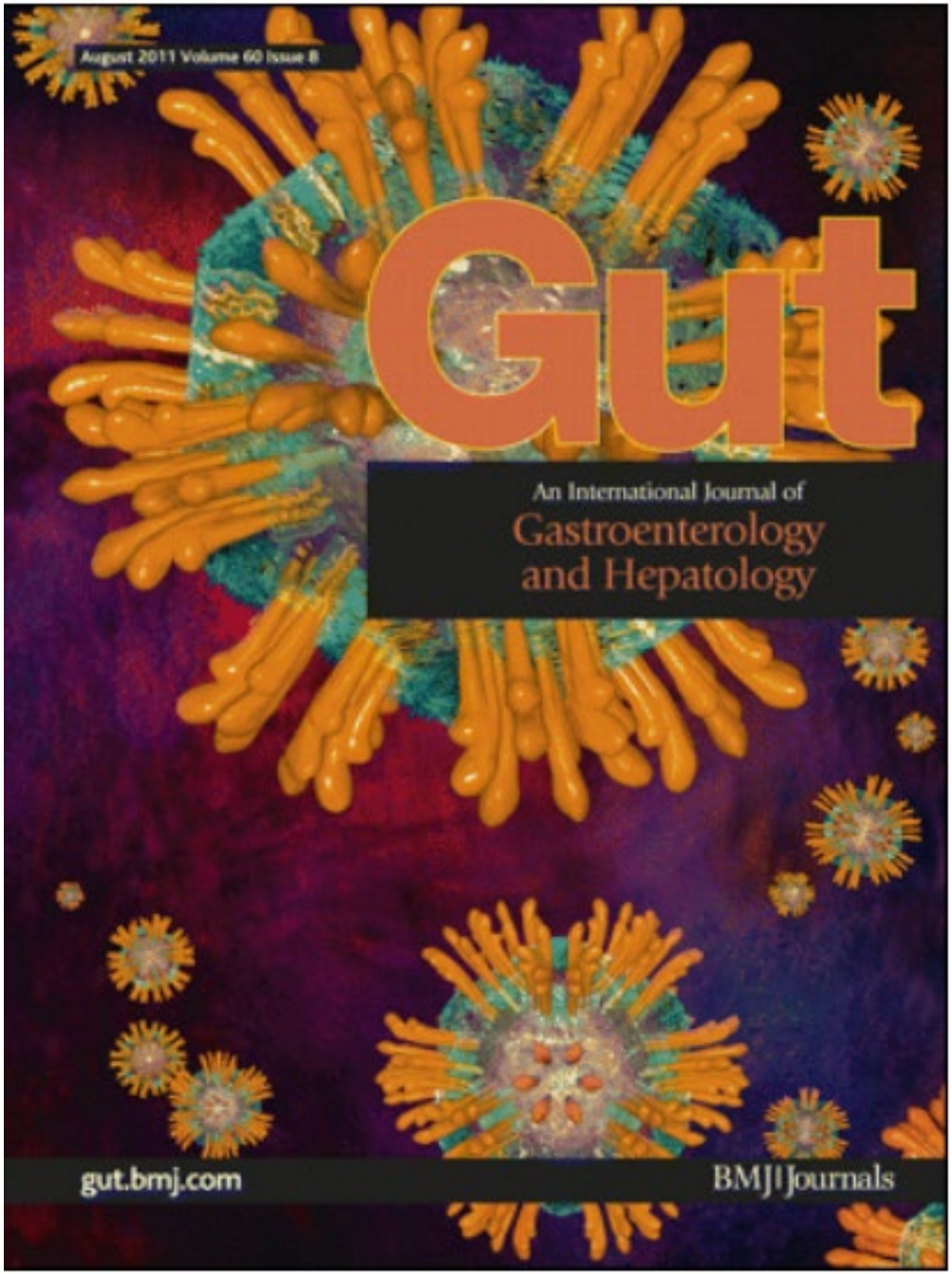
- *Mechanism:* Related to the pharmacologic action (ie, monoclonal antibody targeting α4β7 integrin, a cell surface glycoprotein on B and T lymphocytes that binds to mucosal addressin cell adhesion molecule-1 on the intestinal vasculature) .
- *Risk factors:*
  - Prior anti-TNF use
  - Concurrent narcotic use
  - Older age
  - Concurrent corticosteroid use
  - Cirrhosis



INVESTIGATIONAL THERAPIES

GUT

2011 Aug;60(8)



GUT

2011 Aug;60(8)

Inflammatory bowel disease

The mucosal addressin cell adhesion molecule antibody PF-00547,659 in ulcerative colitis: a randomised study

Séverine Vermeire [1], Subrata Ghosh [2], Julian Panes [3], Jens F Dahlerup [4], Andreas Luegering [5], Jana Sirotiakova [6], Ulrike Strauch [7], Gary Burgess [8], Jacqueline Spanton [8], Steven W Martin [8], Wojciech Niezychowski [8]

Correspondence toDr Séverine Vermeire, Department of Gastroenterology, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium; severine.vermeire@uz.kuleuven.ac.be

Abstract

Background and aims Leucocyte migration to gut mucosa, mediated by integrin binding to mucosal addressin cell adhesion molecule (MAdCAM), is a promising target for therapeutic intervention in inflammatory bowel disease. This first-in-human study of a monoclonal antibody to MAdCAM, PF-00547,659, aimed to explore the safety and preliminary efficacy of this gut-specific mechanism in ulcerative colitis.

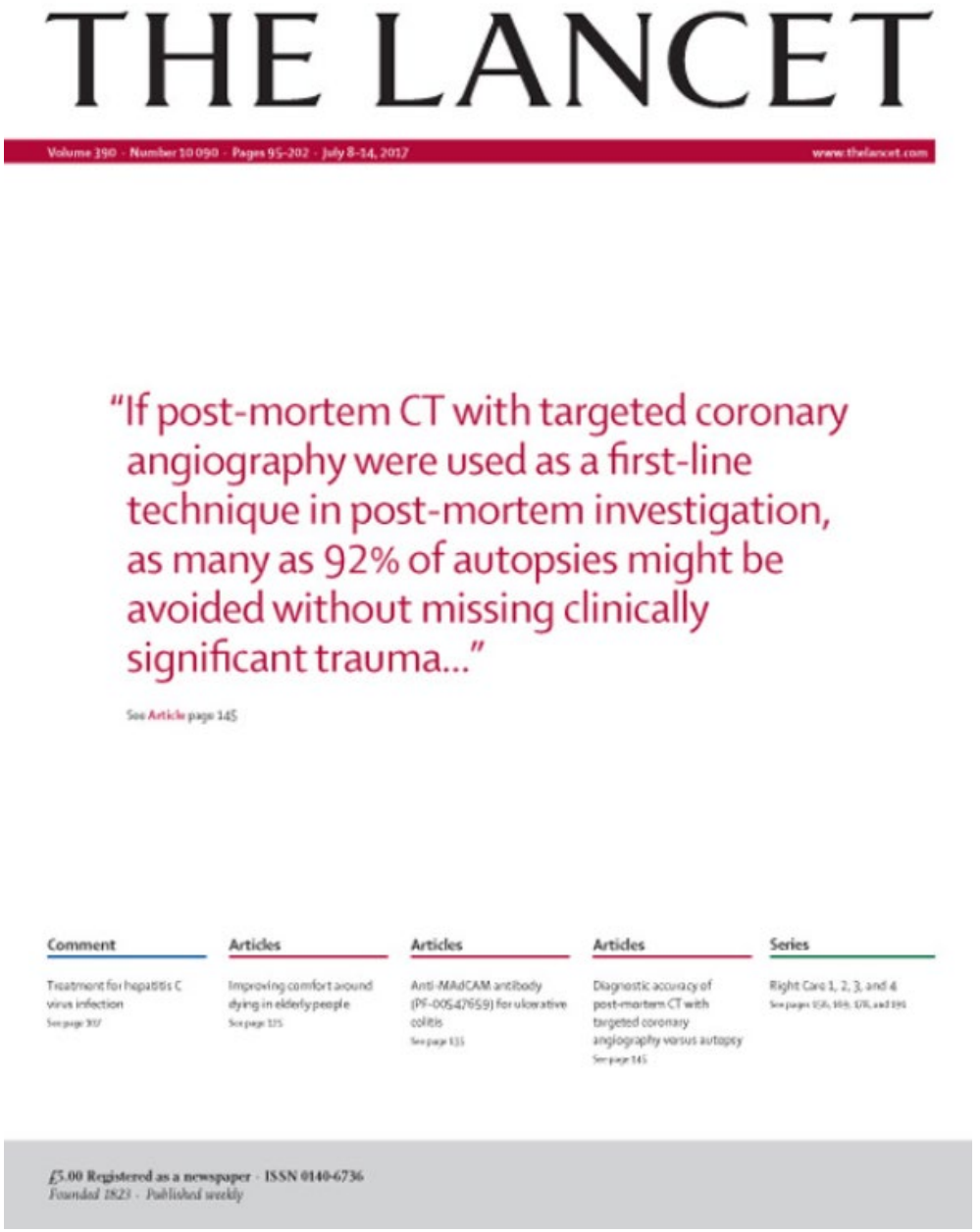
Methods In this randomised, double-blind placebo-controlled study, 80 patients with active ulcerative colitis received single or multiple (three doses, 4-week intervals) doses of PF-00547,659 0.03–10 mg/kg IV/SC, or placebo. Safety was assessed by adverse events, laboratory tests, and immunogenicity. Exploratory efficacy analyses were based on Mayo score and endoscopic responder rates at weeks 4 and 12. Faecal calprotectin was quantified as a measure of disease activity, and the number of $\alpha_4\beta_7^+$ lymphocytes was measured to demonstrate drug activity.

The mucosal addressin cell adhesion molecule antibody PF-00547,659 in ulcerative colitis: a randomised study

- The favourable short-term safety profile and preliminary efficacy findings for PF-00547,659 in this first-in-human study pave the way for further investigation in larger trials, to establish the role of PF-00547,659 in ulcerative colitis treatment

LANCET

Jul 08, 2017



THE LANCET

Volume 390 · Number 10 090 · Pages 95–202 · July 8–14, 2017 www.thelancet.com

"If post-mortem CT with targeted coronary angiography were used as a first-line technique in post-mortem investigation, as many as 92% of autopsies might be avoided without missing clinically significant trauma..."

See Article page 145

Comment

Treatment for hepatitis C virus infection
See page 107

Articles

Improving comfort around dying in elderly people
See page 125

Articles

Anti-MAdCAM antibody (PF-00547659) for ulcerative colitis
See page 135

Articles

Diagnostic accuracy of post-mortem CT with targeted coronary angiography versus autopsy
See page 145

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LANCET

Jul 08, 2017

Clinical Trial > Lancet. 2017 Jul 8;390(10090):135-144. doi: 10.1016/S0140-6736(17)30930-3. Epub 2017 May 17.

Anti-MAdCAM antibody (PF-00547659) for ulcerative colitis (TURANDOT): a phase 2, randomised, double-blind, placebo-controlled trial

Séverine Vermeire [1], William J Sandborn [2], Silvio Danese [3], Xavier Hébuterne [4], Bruce A Salzberg [5], Maria Klopocka [6], Dino Tarabar [7], Tomas Vanasek [8], Miloš Greguš [9], Paul A Hellstern [10], Joo Sung Kim [11], Miles P Sparrow [12], Kenneth J Gorelick [13], Michelle Hinz [13], Alaa Ahmad [13], Vivek Pradhan [13], Mina Hassan-Zahraee [13], Robert Clare [13], Fabio Cataldi [13], Walter Reinisch [14]

Affiliations + expand

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Erratum in

Department of Error.

[No authors listed]

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PMID: 30587368 No abstract available.

Abstract

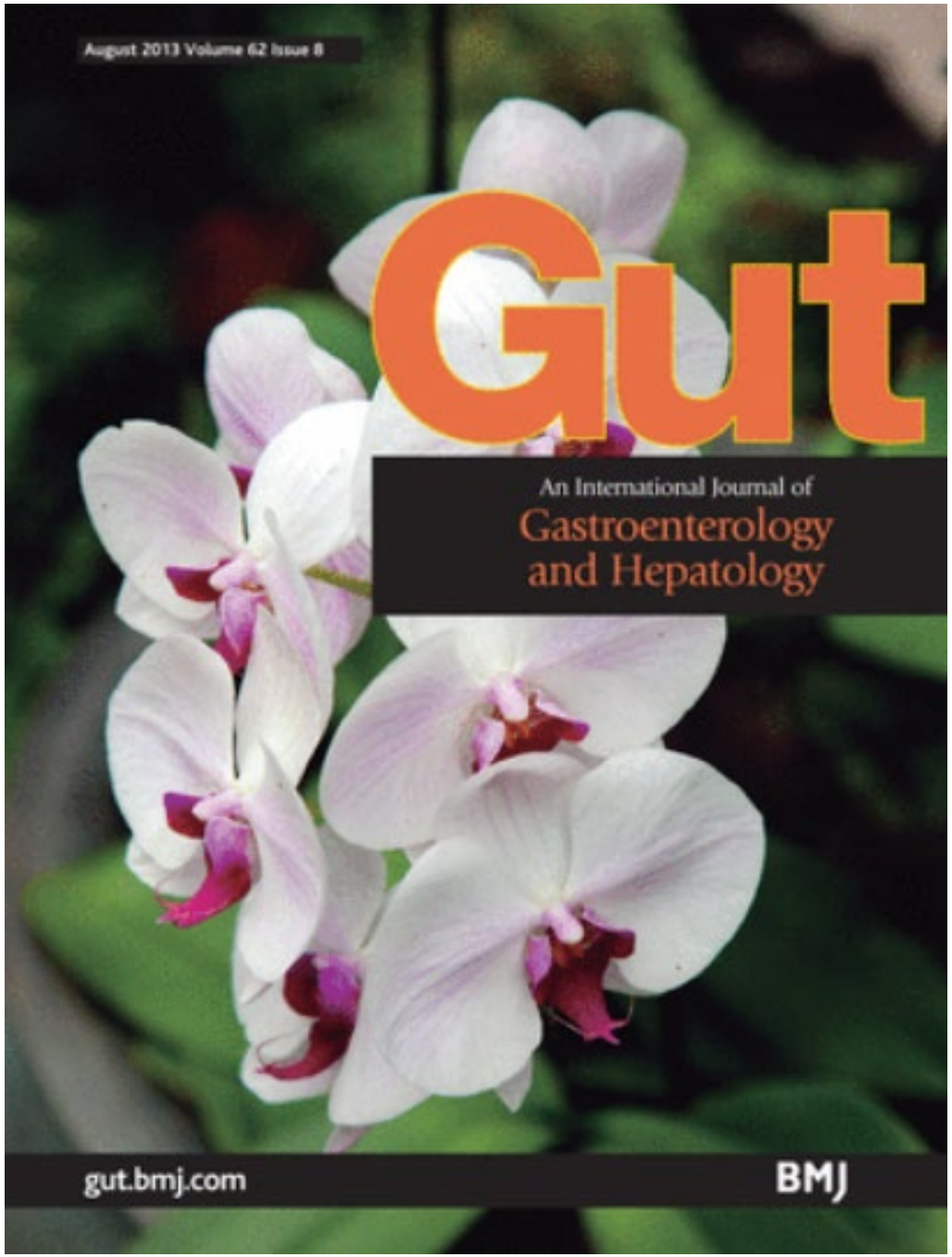
Background: PF-00547659 is a fully human monoclonal antibody that binds to human mucosal addressin cell adhesion molecule-1 (MAdCAM-1) to selectively reduce lymphocyte homing to the intestinal tract. We aimed to assess the efficacy and safety of PF-00547659 in patients with moderate to severe ulcerative colitis.

Anti-MAdCAM antibody (PF-00547659) for ulcerative colitis (TURANDOT): a phase 2, randomised, double-blind, placebo-controlled trial

- F-00547659 was safe and well tolerated in this patient population, and better than placebo for induction of remission in patients with moderate to severe ulcerative colitis.
- The greatest clinical effects were observed with the 22·5 mg and 75 mg doses.

GUT

2013 Aug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and Hepatology
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2013 Aug

OPEN ACCESS

ORIGINAL ARTICLE

A randomised phase I study of etrolizumab (rhuMAb β7) in moderate to severe ulcerative colitis

Paul J Rutgeerts,[1] Richard N Fedorak,[2] Daan W Hommes,[3] Andreas Sturm,[4] Daniel C Baumgart,[4] Brian Bressler,[5] Stefan Schreiber,[6] John C Mansfield,[7] Marna Williams,[8] Meina Tang,[8] Jennifer Visich,[8] Xiaohui Wei,[8] Mary Keir,[8] Diana Luca,[8] Dimitri Danilenko,[8] Jackson Egen,[8] Sharon O'Byrne[8]

► Additional materials are published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2011-301769).

[1]Department of Medicine, Division of Gastroenterology, University of Leuven, Leuven, Belgium
[2]University of Alberta, Edmonton, Alberta, Canada
[3]Center for Inflammatory Bowel Diseases, University of California Los Angeles, Los Angeles, California, USA
[4]U Charité Medical School, Humboldt-University of Berlin, Berlin, Germany
[5]University of British Columbia, Vancouver, British Columbia, Canada
[6]Christian Albrechts University, Kiel, Germany
[7]University of Newcastle upon Tyne, Newcastle upon Tyne, UK
[8]Genentech Research & Early Development, South San Francisco, California, USA

ABSTRACT

Objective Etrolizumab (rhuMAb β7, anti-β7, PRO145223) is a humanised monoclonal antibody targeting the β7 subunit of the heterodimeric integrins α4β7 and αEβ7, which are implicated in leucocyte migration and retention in ulcerative colitis (UC). This randomised phase I study evaluated the safety and pharmacology of etrolizumab in patients with moderate to severe UC.

Design In the single ascending dose (SAD) stage, etrolizumab (0.3, 1.0, 3.0, 10 mg/kg intravenous, 3.0 mg/kg subcutaneous (SC) or placebo) was administered 4:1 (n=25) in each cohort. In the multiple dose (MD) stage, new patients received monthly etrolizumab (0.5 mg/kg SC (n=4), 1.5 mg/kg SC (n=5), 3.0 mg/kg SC (n=4), 4.0 mg/kg intravenous (n=5)) or placebo (n=5). The pharmacokinetics was studied and Mayo Clinic Score evaluated at baseline, day 29 (SAD), and days 43 and 71 (MD).

Results In the SAD stage, there were no dose limiting toxicities, infusion or injection site reactions. Two impaired wound healing serious adverse events occurred in two patients receiving etrolizumab. In the MD stage, there were no dose limiting toxicities, and no infusion or injection site reactions. Headache was the most common adverse event, occurring more often in etrolizumab

Significance of this study

What is already known on this subject?

- Migration of lymphocytes to the gut is a key feature of inflammation in inflammatory bowel disease.
- Selective antimigration therapies are currently developed and specific inhibition of homing of lymphocytes to the gut is currently aimed at for therapy.
- These new therapies target the α4β7–MadCam-1 interaction.

What are the new findings?

- Etrolizumab (antibodies to β7) does inhibit the migration of lymphocytes to the gut and antagonises the retention of lymphocytes in the mucosa by blocking the αEβ7–E-cadherin interaction.
- This phase I study in severe ulcerative colitis shows suitable pharmacokinetics and the early safety of this treatment.
- Clinical improvement of the disease observed in treated patients warrants further phase II

A randomised phase I study of etrolizumab (rhuMAb β7) in moderate to severe ulcerative colitis

- Etrolizumab (rhuMAb β7, anti-β7, PRO145223) is a humanised monoclonal antibody targeting the β7 subunit of the heterodimeric integrins α4β7 and αEβ7, which are implicated in leucocyte migration and retention in ulcerative colitis (UC).
- Etrolizumab is well tolerated in moderate to severe UC. Further investigation is warranted.

LANCET

2014 Jul



LANCET

2014 Jul

Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial

Séverine Vermeire, Sharon O'Byrne, Mary Keir, Marna Williams, Timothy T Lu, John C Mansfield, Christopher A Lamb, Brian G Feagan, Julian Panes, Azucena Salas, Daniel C Baumgart, Stefan Schreiber, Iris Dotan, William J Sandborn, Gaik W Tew, Diana Luca, Meina T Tang, Lauri Diehl, Jeffrey Eastham-Anderson, Gert De Hertogh, Clementine Perrier, Jackson G Egen, John A Kirby, Gert van Assche, Paul Rutgeerts

Summary

Background Etrolizumab is a humanised monoclonal antibody that selectively binds the β7 subunit of the heterodimeric integrins α4β7 and αEβ7. We aimed to assess etrolizumab in patients with moderately-to-severely active ulcerative colitis.

Methods In this double-blind, placebo-controlled, randomised, phase 2 study, patients with moderately-to-severely active ulcerative colitis who had not responded to conventional therapy were recruited from 40 referral centres in 11 countries. Eligible patients (aged 18–75 years; Mayo Clinic Score [MCS] of 5 of higher [or ≥6 in USA]; and disease extending 25 cm or more from anal verge) were randomised (1:1:1) to one of two dose levels of subcutaneous etrolizumab (100 mg at weeks 0, 4, and 8, with placebo at week 2; or 420 mg loading dose [LD] at week 0 followed by 300 mg at weeks 2, 4, and 8), or matching placebo. The primary endpoint was clinical remission at week 10, defined as MCS of 2 or less (with no individual subscore of >1), analysed in the modified intention-to-treat population (mITT; all randomly assigned patients who had received at least one dose of study drug, had at least one post-baseline disease-activity assessment, and had a centrally read screening endoscopic subscore of ≥2). This study is registered with ClinicalTrials.gov, number NCT01336465.

Findings Between Sept 2, 2011, and July 11, 2012, 124 patients were randomly assigned, of whom five had a endoscopic subscore of 0 or 1 and were excluded from the mITT population, leaving 39 patients in the etrolizumab 100 mg group, 39 in the etrolizumab 300 mg plus LD group, and 41 in the placebo group for the primary analyses. No patients in the placebo group had clinical remission at week 10, compared with eight (21% [95% CI 7–36]) patients in the etrolizumab 100 mg group (p=0·0040) and four (10% [0·2–24]) patients in the 300 mg plus LD group (p=0·048). Adverse events occurred in 25 (61%) of 41 patients in the etrolizumab 100 mg group (five [12%] of which were regarded as serious), 19 (48%) of 40 patients in the etrolizumab 300 mg plus LD group (two [5%] serious), and 31 (72%) of 43 patients in the placebo group (five [12%] serious).

Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial

- Etrolizumab was more likely to lead to clinical remission at week 10 than was placebo.
- Therefore, blockade of both α4β7 and αEβ7 might provide a unique therapeutic approach for the treatment of ulcerative colitis, and phase 3 studies have been planned.


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for your attention

NEJM

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ORIGINAL ARTICLE

Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis

William J. Sandborn, M.D., Chinyu Su, M.D., Bruce E. Sands, M.D., Geert R. D'Haens, M.D., Séverine Vermeire, M.D., Ph.D., Stefan Schreiber, M.D., Silvio Danese, M.D., Brian G. Feagan, M.D., Walter Reinisch, M.D., Wojciech Niezychowski, M.D., Gary Friedman, M.D., Nervin Lawendy, Pharm.D., Dahong Yu, M.D., Ph.D., Deborah Woodworth, M.B.A., Arnab Mukherjee, Ph.D., Haiying Zhang, Ph.D., Paul Healey, M.D., and Julian Panés, M.D., for the OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators*

ABSTRACT

BACKGROUND

Tofacitinib, an oral, small-molecule Janus kinase inhibitor, was shown to have potential efficacy as induction therapy for ulcerative colitis in a phase 2 trial. We further evaluated the efficacy of tofacitinib as induction and maintenance therapy.

METHODS

We conducted three phase 3, randomized, double-blind, placebo-controlled trials of tofacitinib therapy in adults with ulcerative colitis. In the OCTAVE Induction 1 and 2 trials, 598 and 541 patients, respectively, who had moderately to severely active ulcerative colitis despite previous conventional therapy or therapy with a tumor necrosis factor antagonist were randomly assigned to receive induction therapy with tofacitinib (10 mg twice daily) or placebo for 8 weeks. The primary end point was remission at 8 weeks. In the OCTAVE Sustain trial, 593 patients who had a clinical response to induction therapy were randomly assigned to receive maintenance therapy with tofacitinib (either 5 mg or 10 mg twice daily) or placebo for 52 weeks. The primary end point was remission at 52 weeks.

RESULTS

In the OCTAVE Induction 1 trial, remission at 8 weeks occurred in 18.5% of the patients in the tofacitinib group versus 8.2% in the placebo group (P=0.007); in the OCTAVE Induction 2 trial, remission occurred in 16.6% versus 3.6% (P<0.001). In the OCTAVE

From the Division of Gastroenterology, Department of Medicine, University of California, San Diego, La Jolla (W.J.S.); Pfizer, Collegeville, PA (C.S., W.N., G.F., N.L., D.Y., D.W., H.Z.); Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York (B.E.S.); the Department of Gastroenterology, Academic Medical Center, Amsterdam (G.R.D.); the Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium (S.V.); Department of Internal Medicine I, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany (S.S.); the Inflammatory Bowel Disease Center, Department of Gastroenterology, Humanitas Research Hospital, Rozzano, Milan (S.D.); Robarts Clinical Trials, Robarts Research Institute, Western University, London (B.G.F.), and McMaster University, Hamilton (W.R.) — both in Ontario, Canada; Pfizer, Groton, CT (A.M., P.H.); and the Networking Biomedical Research Center on Hepatic and Digestive Diseases (CIBERehd), August Pi i Sunyer

Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis

- In patients with moderately to severely active ulcerative colitis, tofacitinib was more effective as induction and maintenance therapy than placebo

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Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials

- Upadacitinib demonstrated a positive efficacy and safety profile and could be an effective treatment option for patients with moderately to severely active ulcerative colitis.