

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 September 14; 23(34): 6197-6370



**EDITORIAL**

- 6197** Defining and predicting deep remission in patients with perianal fistulizing Crohn's disease on anti-tumor necrosis factor therapy

*Papamichael K, Cheifetz AS*

**MINIREVIEWS**

- 6201** Evidences supporting the vascular etiology of post-double balloon enteroscopy pancreatitis: Study in porcine model

*Latorre R, López-Albors O, Soria F, Morcillo E, Esteban P, Pérez-Cuadrado-Robles E, Pérez-Cuadrado-Martínez E*

**ORIGINAL ARTICLE****Basic Study**

- 6212** Circulating inflammatory factors associated with worse long-term prognosis in colorectal cancer

*Olsen RS, Nijm J, Andersson RE, Dimberg J, Wågsäter D*

- 6220** Moxibustion eases chronic inflammatory visceral pain through regulating MEK, ERK and CREB in rats

*Li ZY, Huang Y, Yang YT, Zhang D, Zhao Y, Hong J, Liu J, Wu LJ, Zhang CH, Wu HG, Zhang J, Ma XP*

- 6231** Changes of Ghrelin/GOAT axis and mTOR pathway in the hypothalamus after sleeve gastrectomy in obese type-2 diabetes rats

*Wang Q, Tang W, Rao WS, Song X, Shan CX, Zhang W*

- 6242** Dihydromyricetin-mediated inhibition of the Notch1 pathway induces apoptosis in QGY7701 and HepG2 hepatoma cells

*Lu CJ, He YF, Yuan WZ, Xiang LJ, Zhang J, Liang YR, Duan J, He YH, Li MY*

- 6252** Curcumin inhibits hepatitis B virus infection by down-regulating cccDNA-bound histone acetylation

*Wei ZQ, Zhang YH, Ke CZ, Chen HX, Ren P, He YL, Hu P, Ma DQ, Luo J, Meng ZJ*

**Retrospective Cohort Study**

- 6261** Systemic immune-inflammation index for predicting prognosis of colorectal cancer

*Chen JH, Zhai ET, Yuan YJ, Wu KM, Xu JB, Peng JJ, Chen CQ, He YL, Cai SR*

**Retrospective Study**

- 6273** Predictive factors for the failure of endoscopic stent-in-stent self-expandable metallic stent placement to treat malignant hilar biliary obstruction

*Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Watanabe K, Nakamura J, Kikuchi H, Waragai Y, Takasumi M, Sato Y, Hikichi T, Ohira H*

- 6281 Assessment of colon polyp morphology: Is education effective?

*Kim JH, Nam KS, Kwon HJ, Choi YJ, Jung K, Kim SE, Moon W, Park MI, Park SJ*

- 6287 Body mass index does not affect the survival of pancreatic cancer patients

*Jiang QL, Wang CF, Tian YT, Huang H, Zhang SS, Zhao DB, Ma J, Yuan W, Sun YM, Che X, Zhang JW, Chu YM, Zhang YW, Chen YT*

### Observational Study

- 6294 Access to biologicals in Crohn's disease in ten European countries

*Péntek M, Lakatos PL, Oorsprong T, Gulácsi L, Pavlova M, Groot W, Rencz F, Brodsky V, Baji P; Crohn's Disease Research Group*

- 6306 Temporal trends in the misdiagnosis rates between Crohn's disease and intestinal tuberculosis

*Seo H, Lee S, So H, Kim D, Kim SO, Soh JS, Bae JH, Lee SH, Hwang SW, Park SH, Yang DH, Kim KJ, Byeon JS, Myung SJ, Yang SK, Ye BD*

- 6315 Detection of metastatic cancer cells in mesentery of colorectal cancer patients

*Luo XL, Xie DX, Wu JX, Wu AD, Ge ZQ, Li HJ, Hu JB, Cao ZX, Gong JP*

- 6321 Natural history of covert hepatic encephalopathy: An observational study of 366 cirrhotic patients

*Wang AJ, Peng AP, Li BM, Gan N, Pei L, Zheng XL, Hong JB, Xiao HY, Zhong JW, Zhu X*

### Randomized Controlled Trial

- 6330 Circular RNA hsa\_circ\_0000745 may serve as a diagnostic marker for gastric cancer

*Huang M, He Yr, Liang LC, Huang Q, Zhu ZQ*

- 6339 P2Y1R is involved in visceral hypersensitivity in rats with experimental irritable bowel syndrome

*Wu J, Cheng Y, Zhang R, Liu D, Luo YM, Chen KL, Ren S, Zhang J*

- 6350 Randomized controlled trial of uncut Roux-en-Y vs Billroth II reconstruction after distal gastrectomy for gastric cancer: Which technique is better for avoiding biliary reflux and gastritis?

*Yang D, He L, Tong WH, Jia ZF, Su TR, Wang Q*

### Randomized Clinical Trial

- 6357 Drainage fluid and serum amylase levels accurately predict development of postoperative pancreatic fistula

*Jin S, Shi XJ, Wang SY, Zhang P, Lv GY, Du XH, Wang GY*

### CASE REPORT

- 6365 Interventional endoscopic ultrasound for a symptomatic pseudocyst secondary to gastric heterotopic pancreas

*Jin HB, Lu L, Yang JF, Lou QF, Yang J, Shen HZ, Tang XW, Zhang XF*

**ABOUT COVER**

Editorial board member of *World Journal of Gastroenterology*, Gabriele Grassi, MD, PhD, Associate Professor, Department of Life Sciences, University Hospital of Cattinara, 34149 Trieste, Italy

**AIMS AND SCOPE**

*World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7<sup>th</sup>, 14<sup>th</sup>, 21<sup>st</sup>, and 28<sup>th</sup> each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

**INDEXING/ABSTRACTING**

*World Journal of Gastroenterology* (*WJG*) is now indexed in Current Contents<sup>®</sup>/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch<sup>®</sup>), Journal Citation Reports<sup>®</sup>, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports<sup>®</sup> cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29<sup>th</sup> among 79 journals in gastroenterology and hepatology (quartile in category Q2).

**FLYLEAF**

**I-IX Editorial Board**

**EDITORS FOR THIS ISSUE**

**Responsible Assistant Editor:** *Xiang Li*  
**Responsible Electronic Editor:** *Fen-Fen Zhang*  
**Proofing Editor-in-Chief:** *Lian-Sheng Ma*

**Responsible Science Editor:** *Ke Chen*  
**Proofing Editorial Office Director:** *Jin-Lei Wang*

**NAME OF JOURNAL**  
*World Journal of Gastroenterology*

**ISSN**  
ISSN 1007-9327 (print)  
ISSN 2219-2840 (online)

**LAUNCH DATE**  
October 1, 1995

**FREQUENCY**  
Weekly

**EDITORS-IN-CHIEF**  
**Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon**, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

**Stephen C Strom, PhD, Professor**, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

**Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology**, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach,

CA 90822, United States

**EDITORIAL BOARD MEMBERS**  
All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

**EDITORIAL OFFICE**  
Jin-Lei Wang, Director  
Yuan Qi, Vice Director  
Ze-Mao Gong, Vice Director  
*World Journal of Gastroenterology*  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLISHER**  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>

<http://www.wjgnet.com>

**PUBLICATION DATE**  
September 14, 2017

**COPYRIGHT**  
© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

**SPECIAL STATEMENT**  
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

**INSTRUCTIONS TO AUTHORS**  
Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

**ONLINE SUBMISSION**  
<http://www.f6publishing.com>



## Defining and predicting deep remission in patients with perianal fistulizing Crohn's disease on anti-tumor necrosis factor therapy

Konstantinos Papamichael, Adam S Cheifetz

Konstantinos Papamichael, Adam S Cheifetz, Center for Inflammatory Bowel Diseases, Division of Gastroenterology, Beth-Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, United States

ORCID number: Konstantinos Papamichael (0000-0003-1497-0254); Adam S Cheifetz (0000-0002-6010-1896).

**Author contributions:** Papamichael K wrote the manuscript; Cheifetz AS contributed to the manuscript critical revision; all authors approved the final version of the article.

**Conflict-of-interest statement:** Papamichael K has nothing to disclose; Cheifetz AS has received consultancy fees from AbbVie, Janssen, Takeda, Ferring, AMAG, Miraca and Pfizer.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to:** Konstantinos Papamichael, MD, PhD, FEBGH, Center for Inflammatory Bowel Diseases, Division of Gastroenterology, Beth-Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave., Boston, MA 02215, United States. [kpapamic@bidmc.harvard.edu](mailto:kpapamic@bidmc.harvard.edu)  
Telephone: +1-617-6672802  
Fax: +1-617-6675826

Received: July 28, 2017  
Peer-review started: July 28, 2017  
First decision: August 10, 2017  
Revised: August 16, 2017  
Accepted: September 5, 2017  
Article in press: September 5, 2017

Published online: September 14, 2017

### Abstract

Perianal fistulas can occur to up to one-third of patients with Crohn's disease (CD) leading to significant disabling disease and morbidity. Fistulising perianal CD treatment often necessitates a combined pharmacological and surgical approach. Anti-tumor necrosis factor (anti-TNF) therapy, particularly infliximab, has been shown to be very effective for both perianal and internal fistulising CD. Nevertheless, current data suggest that sustained remission and long-term complete fistula healing can be achieved in only 30% to 50% of patients. Moreover, these percentages refer mostly to clinical rather than deep remission, defined as endoscopic and radiologic remission, which is quickly emerging as the preferred goal of therapy. Unfortunately, the therapeutic options for perianal fistulising CD are still limited. As such, it would be of great value to be able to predict, and more importantly, prevent treatment failure in these patients by early and continued optimization of anti-TNF therapy. Similar to ulcerative colitis and luminal CD, recent data demonstrate that higher infliximab concentrations are associated with better clinical outcomes in patients with perianal fistulising CD. This suggests that therapeutic drug monitoring and a treat-to-trough therapeutic approach may emerge as the new standard of care for optimizing anti-TNF therapy in patients with perianal fistulising CD.

**Key words:** Inflammatory bowel disease; Infliximab; Adalimumab; Magnetic resonance imaging; Drug monitoring; Fistula healing

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Defining and predicting deep remission is important to guide the management of patients with perianal fistulizing Crohn's disease (CD). Deep remission, defined as complete fistula healing based on objective endoscopic and radiologic findings, should be the goal of care in the treatment of patients with perianal CD. Currently, anti-tumor necrosis factor (anti-TNF) are the standard of care for perianal CD, but long-term outcomes are disappointing. Data suggests that higher infliximab concentrations are associated with better clinical outcomes in patients with perianal fistulizing CD and thus therapeutic drug monitoring may be a valid therapeutic strategy for optimizing anti-TNF therapy towards improved objective outcomes and deep remission.

Papamichael K, Cheifetz AS. Defining and predicting deep remission in patients with perianal fistulizing Crohn's disease on anti-tumor necrosis factor therapy. *World J Gastroenterol* 2017; 23(34): 6197-6200 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i34/6197.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i34.6197>

## INTRODUCTION

Perianal fistulas can develop to up to one-third of patients with Crohn's disease (CD) leading to disabling disease, morbidity, and a significant impairment in quality of life<sup>[1]</sup>. The treatment of fistulizing perianal CD is not simple and often requires a multidisciplinary approach of both pharmacological and surgical therapy especially for complex perianal fistulae<sup>[2]</sup>. Anti-tumor necrosis factor (anti-TNF) therapy has revolutionized the treatment of both perianal and internal fistulizing CD<sup>[3-18]</sup>. Nevertheless, therapeutic outcomes from randomised controlled trials (RCTs), post-hoc analyses of RCTs and real-life prospective or retrospective studies show that long-term remission can be achieved in only 30%-50% of patients (Table 1). Moreover, these percentages refer mostly to clinical remission, based on symptoms and physician global assessment (PGA), and not to objective endoscopic and/or radiological healing. At this time, the preferred goal of treatment should be deep remission, or the combination of clinical and the more objective measures, including radiologic and endoscopic healing. As therapeutic options for perianal fistulizing CD are still limited it is very important to attempt to predict and subsequently prevent treatment failure in these patients. Preliminary data demonstrate that higher infliximab concentrations are associated with improved clinical outcomes in patients with perianal fistulizing CD, suggesting that therapeutic drug monitoring (TDM) and a treat-to-trough approach is likely a valid therapeutic strategy for optimizing anti-TNF therapy in

these patients<sup>[19,20]</sup>.

## Defining deep remission

Most studies typically use clinical remission, defined as absence of any draining fistulas based on PGA and patients' reports, as a therapeutic endpoint for perianal fistulizing CD<sup>[3-18]</sup>. Nevertheless, deep remission, defined as mucosal and/or radiological healing of fistulas, is likely a more appropriate goal of therapy for perianal fistulizing CD. T2-weighted magnetic resonance imaging (MRI) with fat-suppression is considered the gold-standard for fistula imaging and an MRI-based score is currently available for defining disease activity, although it is still not widely used in clinical practice<sup>[1]</sup>. Thomassin *et al.*<sup>[11]</sup> have recently showed that deep remission, defined as a composite clinical (absence of any draining fistulas and self-reported drainage episodes by the patient at two successive evaluations), endoscopic (absence of ulcers in the anal canal) and radiological (absence of T2 hyperintensity and contrast enhancement on MRI) remission, was achieved in approximately one-third of patients with perianal fistulizing CD<sup>[11]</sup>.

## Predicting deep remission

As new drugs for the treatment of perianal fistulizing CD are still awaited, it is important to be able to predict who will achieve deep remission and who will not respond adequately to typical anti-TNF dosing and will require early (and continued) optimization<sup>[1,2]</sup>. Although several variables have been associated with improved outcomes (Table 2), prediction of deep remission remains a challenge. Thomassin *et al.*<sup>[11]</sup> have recently identified absence of rectal involvement on MRI (OR = 4.6; 95%CI: 1.03-20.5) as the only variable associated with deep remission in patients with perianal fistulizing CD<sup>[11]</sup>. Similar to ulcerative colitis and luminal CD<sup>[19-25]</sup>, recent data demonstrate that higher infliximab concentrations are associated with better clinical outcomes in patients with perianal fistulizing CD<sup>[26,27]</sup>. Regarding maintenance therapy Yarur *et al.*<sup>[26]</sup> recently showed that infliximab trough concentrations  $\geq 10.1$   $\mu\text{g/mL}$  are associated with fistula healing and based on quartile analyses proposed that physicians should aim for even higher concentrations ( $> 20.2$   $\mu\text{g/mL}$ ) before giving up and moving on to alternative therapies with a different mechanism of action.

## CONCLUSION

Deep remission defined as a composite clinical, endoscopic and radiological remission should really be considered the goal of therapy in patients with perianal fistulizing CD. TDM may be a valid therapeutic strategy for optimising anti-TNF therapy, improving therapeutic outcomes, and moving towards more personalized medical care.

**Table 1 Long-term outcomes of patients with perianal fistulizing Crohn's disease on anti-tumor necrosis factor maintenance therapy**

Type of anti-TNF therapy	n	Complex fistulas, %	Follow up, wk	Therapeutic outcome of interest	Therapeutic outcome, %	Ref.
IFX	68	75	52	Complete fistula closure & CDAI < 150	34	[4]
IFX	59	85	> 56	Complete fistula closure (PGA)	41	[5]
IFX	13	ND	95 <sup>1</sup>	Reduction of fistulas number (MRI)	15	[5]
IFX	156	82	250 <sup>1</sup>	At least 1 fistula closure	69	[6]
IFX	12	ND	156	Clinical remission (PGA)	33	[7]
IFX	12	ND	156	Radiological healing (MRI)	42	[7]
IFX	19	ND	52	Absence of draining fistulas (PGA)	53	[8]
IFX	26	69	255 <sup>2</sup>	Complete fistula closure	42	[9]
IFX (RCT)	96	ND	54	Complete fistula closure	36	[10]
IFX/ADM	49	ND	160 <sup>2</sup>	Deep remission (PGA, MRI, endoscopy)	33	[11]
IFX/ADM	49	ND	160 <sup>2</sup>	Absence of draining fistulas (PGA)	53	[11]
IFX/ADM	20	ND	52	Absence of draining fistulas (PGA)	35	[12]
IFX/ADM	78	67	192 <sup>1</sup>	Absence of drainage with seton removal	53	[13]
IFX/ADM	20	ND	78	Radiological healing (MRI)	30	[8]
ADM	7	ND	156	Absence of draining fistulas (PGA)	0	[7]
ADM	7	ND	156	Radiological healing (MRI)	14	[7]
ADM	7	ND	52	Absence of draining fistulas (PGA)	29	[8]
ADM	39	ND	52	Clinical remission (FDAI)	41	[14]
ADM	14	ND	52	Radiological healing (MRI)	43	[14]
ADM	53	ND	40	Complete fistula closure	41	[15]
ADM (RCT)	70	ND	56	Absence of draining fistulas (PGA)	33	[16]
ADM (post hoc)	70	ND	116	Absence of draining fistulas (PGA)	31	[17]
CZP (RCT)	28	ND	26	Complete fistula closure	36	[18]

<sup>1</sup>Median; <sup>2</sup>Mean. CDAI: Crohn's disease activity index; TNF: Tumor necrosis factor; ADM: Adalimumab; IFX: Infliximab; CZP: Certolizumab pegol; RCT: Randomized controlled trial; PGA: Physician global assessment; ND: Not defined; FDAI: Fistula drainage assessment index; MRI: Magnetic resonance imaging.

**Table 2 Variables associated with improved therapeutic outcomes of anti-tumor necrosis factor maintenance therapy in patients with perianal fistulizing Crohn's disease**

Variables	Ref.
Clinical or phenotypic	
Ileocolonic disease	[6]
Concomitant immunosuppressants	[6]
Duration of seton drainage (< 34 wk)	[6]
Duration of infliximab treatment (> 118 wk)	[6]
Number of infliximab infusions (> 19)	[6]
Absence of complex fistulas	[14]
Male gender	[26]
Absence of switch of anti-TNF therapy	[11]
Imaging	
Absence of persisting fistulas on MRI	[5]
Absence of collections at baseline on MRI	[5]
Absence of rectal wall involvement on MRI	[5]
Absence of single-branched fistulas on MRI	[5]
Absence of rectal involvement on MRI	[11]
Serologic	
Infliximab (maintenance) trough concentrations $\geq 10.1 \mu\text{g/mL}$	[26]
Endoscopic	
Absence of active proctitis	[11]

TNF: Tumor necrosis factor; MRI: Magnetic resonance imaging.

## REFERENCES

- Gecse KB, Sebastian S, Hertogh Gd, Yassin NA, Kotze PG, Reinisch W, Spinelli A, Koutroubakis IE, Katsanos KH, Hart A, van den Brink GR, Rogler G, Bemelman WA. Results of the Fifth Scientific Workshop of the ECCO [II]: Clinical Aspects of Perianal Fistulizing Crohn's Disease-the Unmet Needs. *J Crohns Colitis* 2016; **10**: 758-765 [PMID: 26826183 DOI: 10.1093/ecco-jcc/jjw039]
- Gecse KB, Bemelman W, Kamm MA, Stoker J, Khanna R, Ng SC, Panés J, van Assche G, Liu Z, Hart A, Levesque BG, D'Haens G; World Gastroenterology Organization, International Organisation for Inflammatory Bowel Diseases IOIBD, European Society of Coloproctology and Roberts Clinical Trials; World Gastroenterology Organization International Organisation for Inflammatory Bowel Diseases IOIBD European Society of Coloproctology and Roberts Clinical Trials. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut* 2014; **63**: 1381-1392 [PMID: 24951257 DOI: 10.1136/gutjnl-2013-306709]
- Amiot A, Setakhr V, Seksik P, Allez M, Treton X, De Vos M, Laharie D, Colombel JF, Abitbol V, Reimund JM, Moreau J, Veyrac M, Flourie B, Cosnes J, Lemann M, Bouhnik Y. Long-term outcome of enterocutaneous fistula in patients with Crohn's disease treated with anti-TNF therapy: a cohort study from the GETAID. *Am J Gastroenterol* 2014; **109**: 1443-1449 [PMID: 25091063 DOI: 10.1038/ajg.2014.183]
- Bor R, Farkas K, Bálint A, Szucs M, Ábrahám S, Baradnay G, Wittmann T, Szepes Z, Nagy F, Molnár T. Efficacy of combined anti-TNF-alpha and surgical therapy in perianal and enterocutaneous fistulizing Crohn's disease--clinical observations from a tertiary Eastern European center. *Scand J Gastroenterol* 2015; **50**: 182-187 [PMID: 25384713 DOI: 10.3109/00365521.2014.936033]
- Karmiris K, Bielen D, Vanbeckevoort D, Vermeire S, Coremans G, Rutgeerts P, Van Assche G. Long-term monitoring of infliximab therapy for perianal fistulizing Crohn's disease by using magnetic resonance imaging. *Clin Gastroenterol Hepatol* 2011; **9**: 130-136 [PMID: 21056696 DOI: 10.1016/j.cgh.2010.10.022]
- Bouguen G, Siproudhis L, Bretagne JF, Bigard MA, Peyrin-Biroulet L. Nonfistulizing perianal Crohn's disease: clinical features, epidemiology, and treatment. *Inflamm Bowel Dis* 2010; **16**: 1431-1442 [PMID: 20310013 DOI: 10.1002/ibd.21261]
- Tozer P, Ng SC, Siddiqui MR, Plamondon S, Burling D, Gupta A, Swatton A, Tripoli S, Vaizey CJ, Kamm MA, Phillips R, Hart

- A. Long-term MRI-guided combined anti-TNF- $\alpha$  and thiopurine therapy for Crohn's perianal fistulas. *Inflamm Bowel Dis* 2012; **18**: 1825-1834 [PMID: 22223472 DOI: 10.1002/ibd.21940]
- 8 Ng SC, Plamondon S, Gupta A, Burling D, Swatton A, Vaizey CJ, Kamm MA. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas. *Am J Gastroenterol* 2009; **104**: 2973-2986 [PMID: 19755971 DOI: 10.1038/ajg.2009.509]
- 9 Tougeron D, Savoye G, Savoye-Collet C, Koning E, Michot F, Lerebours E. Predicting factors of fistula healing and clinical remission after infliximab-based combined therapy for perianal fistulizing Crohn's disease. *Dig Dis Sci* 2009; **54**: 1746-1752 [PMID: 19003531 DOI: 10.1007/s10620-008-0545-y]
- 10 Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350**: 876-885 [PMID: 14985485 DOI: 10.1056/NEJMoa030815]
- 11 Thomassin L, Armengol-Debeir L, Charpentier C, Bridoux V, Koning E, Savoye G, Savoye-Collet C. Magnetic resonance imaging may predict deep remission in patients with perianal fistulizing Crohn's disease. *World J Gastroenterol* 2017; **23**: 4285-4292 [PMID: 28694669 DOI: 10.3748/wjg.v23.i23.4285]
- 12 Savoye-Collet C, Savoye G, Koning E, Dacher JN, Lerebours E. Fistulizing perianal Crohn's disease: contrast-enhanced magnetic resonance imaging assessment at 1 year on maintenance anti-TNF- $\alpha$  therapy. *Inflamm Bowel Dis* 2011; **17**: 1751-1758 [PMID: 21744430 DOI: 10.1002/ibd.21568]
- 13 Kotze PG, Albuquerque IC, da Luz Moreira A, Tonini WB, Olandoski M, Coy CS. Perianal complete remission with combined therapy (seton placement and anti-TNF agents) in Crohn's disease: a Brazilian multicenter observational study. *Arq Gastroenterol* 2014; **51**: 284-289 [PMID: 25591155 DOI: 10.1590/S0004-28032014000400004]
- 14 Castaño-Milla C, Chaparro M, Saro C, Barreiro-de Acosta M, García-Albert AM, Bujanda L, Martín-Arranz MD, Carpio D, Muñoz F, Manceño N, García-Planella E, Piqueras M, Calvet X, Cabriada JL, Botella B, Bermejo F, Gisbert JP. Effectiveness of adalimumab in perianal fistulas in Crohn's disease patients naive to anti-TNF therapy. *J Clin Gastroenterol* 2015; **49**: 34-40 [PMID: 25485513 DOI: 10.1097/MCG.0000000000000169]
- 15 Fortea-Ormaechea JI, González-Lama Y, Casis B, Chaparro M, López Serrano P, Van Domselaar M, Bermejo F, Pajares R, Ponferrada A, Vera MI, Martínez Montiel P, Gisbert JP, Pérez-Calle JL, López San Román A, Abreu L, Menchén LA, Marín-Jiménez I. Adalimumab is effective in long-term real life clinical practice in both luminal and perianal Crohn's disease. The Madrid experience. *Gastroenterol Hepatol* 2011; **34**: 443-448 [PMID: 21724297 DOI: 10.1016/j.gastrohep.2011.04.001]
- 16 Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132**: 52-65 [PMID: 17241859 DOI: 10.1053/j.gastro.2006.11.041]
- 17 Colombel JF, Schwartz DA, Sandborn WJ, Kamm MA, D'Haens G, Rutgeerts P, Enns R, Panaccione R, Schreiber S, Li J, Kent JD, Lomax KG, Pollack PF. Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut* 2009; **58**: 940-948 [PMID: 19201775 DOI: 10.1136/gut.2008.159251]
- 18 Schreiber S, Lawrance IC, Thomsen OØ, Hanauer SB, Bloomfield R, Sandborn WJ. Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease - subgroup results from a placebo-controlled study. *Aliment Pharmacol Ther* 2011; **33**: 185-193 [PMID: 21083671 DOI: 10.1111/j.1365-2036.2010.04509.x]
- 19 Papamichael K, Chachu KA, Vajravelu RK, Vaughn BP, Ni J, Osterman MT, Cheifetz AS. Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab. *Clin Gastroenterol Hepatol* 2017; pii: S1542-3565(17)30385-3 [PMID: 28365486 DOI: 10.1016/j.cgh.2017.03.031]
- 20 Van Stappen T, Bollen L, Vande Casteele N, Papamichael K, Van Assche G, Ferrante M, Vermeire S, Gils A. Rapid Test for Infliximab Drug Concentration Allows Immediate Dose Adaptation. *Clin Transl Gastroenterol* 2016; **7**: e206 [PMID: 27929524 DOI: 10.1038/ctg.2016.62]
- 21 Papamichael K, Van Stappen T, Vande Casteele N, Gils A, Billiet T, Tops S, Claes K, Van Assche G, Rutgeerts P, Vermeire S, Ferrante M. Infliximab Concentration Thresholds During Induction Therapy Are Associated With Short-term Mucosal Healing in Patients With Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2016; **14**: 543-549 [PMID: 26681486 DOI: 10.1016/j.cgh.2015.11.014]
- 22 Ungar B, Levy I, Yavne Y, Yavzori M, Picard O, Fudim E, Loebstein R, Chowers Y, Eliakim R, Kopylov U, Ben-Horin S. Optimizing Anti-TNF- $\alpha$  Therapy: Serum Levels of Infliximab and Adalimumab Are Associated With Mucosal Healing in Patients With Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol* 2016; **14**: 550-557.e2 [PMID: 26538204 DOI: 10.1016/j.cgh.2015.10.025]
- 23 Ward MG, Warner B, Unsworth N, Chuah SW, Brownclark C, Shieh S, Parkes M, Sanderson JD, Arkir Z, Reynolds J, Gibson PR, Irving PM. Infliximab and adalimumab drug levels in Crohn's disease: contrasting associations with disease activity and influencing factors. *Aliment Pharmacol Ther* 2017; **46**: 150-161 [PMID: 28481014 DOI: 10.1111/apt.14124]
- 24 Roblin X, Marotte H, Leclerc M, Del Tedesco E, Phelip JM, Peyrin-Biroulet L, Paul S. Combination of C-reactive protein, infliximab trough levels, and stable but not transient antibodies to infliximab are associated with loss of response to infliximab in inflammatory bowel disease. *J Crohns Colitis* 2015; **9**: 525-531 [PMID: 25895875 DOI: 10.1093/ecco-jcc/jjv061]
- 25 Paul S, Del Tedesco E, Marotte H, Rinaudo-Gaujous M, Moreau A, Phelip JM, Genin C, Peyrin-Biroulet L, Roblin X. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis* 2013; **19**: 2568-2576 [PMID: 24013361 DOI: 10.1097/MIB.0b013e3182a77b41]
- 26 Yarur AJ, Kanagala V, Stein DJ, Czul F, Quintero MA, Agrawal D, Patel A, Best K, Fox C, Idstein K, Abreu MT. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther* 2017; **45**: 933-940 [PMID: 28211593 DOI: 10.1111/apt.13970]
- 27 Davidov Y, Ungar B, Bar-Yoseph H, Carter D, Haj-Natour O, Yavzori M, Chowers Y, Eliakim R, Ben-Horin S, Kopylov U. Association of Induction Infliximab Levels With Clinical Response in Perianal Crohn's Disease. *J Crohns Colitis* 2017; **11**: 549-555 [PMID: 28453755 DOI: 10.1093/ecco-jcc/jjw182]

P- Reviewer: Lakatos PL, Negreanu N, Walter F S- Editor: Ma YJ  
L- Editor: A E- Editor: Zhang FF







Published by **Baishideng Publishing Group Inc**  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-223-8242  
Fax: +1-925-223-8243  
E-mail: [bpgooffice@wjgnet.com](mailto:bpgooffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>



ISSN 1007-9327

