

World Journal of *Gastroenterology*

World J Gastroenterol 2018 September 28; 24(36): 4093-4216



**EDITORIAL**

- 4093** Interleukin 12/interleukin 23 pathway: Biological basis and therapeutic effect in patients with Crohn's disease
Aggeletopoulou I, Assimakopoulos SF, Konstantakis C, Triantos C

REVIEW

- 4104** Role of microRNAs in alcohol-induced liver disorders and non-alcoholic fatty liver disease
Torres JL, Novo-Veleiro I, Manzanedo L, Alvela-Suárez L, Macías R, Laso FJ, Marcos M
- 4119** Calcium-sensing receptor in colorectal inflammation and cancer: Current insights and future perspectives
Iamartino L, Elajna T, Kallay E, Schepelmann M
- 4132** Production of extracellular lysophosphatidic acid in the regulation of adipocyte functions and liver fibrosis
Yang F, Chen GX

MINIREVIEWS

- 4152** Ten years of sorafenib in hepatocellular carcinoma: Are there any predictive and/or prognostic markers?
Marisi G, Cucchetti A, Ulivi P, Canale M, Cabibbo G, Solaini L, Foschi FG, De Matteis S, Ercolani G, Valgiusti M, Frassinetti GL, Scartozzi M, Casadei Gardini A

ORIGINAL ARTICLE**Basic Study**

- 4164** Differential expression of mucin 1 and mucin 2 in colorectal cancer
Kasprzak A, Siodla E, Andrzejewska M, Szmaja J, Seraszek-Jaros A, Cofta S, Szaflarski W
- 4178** Mechanism of combined use of vitamin D and puerarin in anti-hepatic fibrosis by regulating the Wnt/ β -catenin signalling pathway
Huang GR, Wei SJ, Huang YQ, Xing W, Wang LY, Liang LL

Retrospective Study

- 4186** Frequency, types and treatment of anemia in Turkish patients with inflammatory bowel disease
Bengi G, Keyvan H, Durmaz SB, Akpınar H

Prospective Study

- 4197** Low-dose spectral insufflation computed tomography protocol preoperatively optimized for T stage esophageal cancer - preliminary research experience
Zhou Y, Liu D, Hou P, Zha KJ, Wang F, Zhou K, He W, Gao JB

CASE REPORT

- 4208** Novel methionyl-tRNA synthetase gene variants/phenotypes in interstitial lung and liver disease: A case report and review of literature
Abuduxikuer K, Feng JY, Lu Y, Xie XB, Chen L, Wang JS

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Matthias Ocker, MD, Professor, Department of Oncology Translational Medicine, Bayer AG, Berlin 13353, Germany

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 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 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[®]/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch[®]), Journal Citation Reports[®], Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports[®] cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Yan Huang*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Rao-Yu Ma*
Proofing Editorial Office Director: *Ze-Mao Gong*

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

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

Ze-Mao Gong, 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
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
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLICATION DATE

September 28, 2018

COPYRIGHT

© 2018 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>

Interleukin 12/interleukin 23 pathway: Biological basis and therapeutic effect in patients with Crohn's disease

Ioanna Aggeletopoulou, Stelios F Assimakopoulos, Christos Konstantakis, Christos Triantos

Ioanna Aggeletopoulou, Christos Konstantakis, Christos Triantos, Division of Gastroenterology, Department of Internal Medicine, Medical School, University of Patras, Patras 26504, Greece

Stelios F Assimakopoulos, Department of Internal Medicine, University Hospital of Patras, Patras 26504, Greece

ORCID number: Ioanna Aggeletopoulou (0000-0003-4489-1485); Stelios F Assimakopoulos (0000-0002-6901-3681); Christos Konstantakis (0000-0001-5834-9182); Christos Triantos (0000-0003-3094-8209).

Author contributions: Aggeletopoulou I and Konstantakis C were responsible for the literature review and analysis; Aggeletopoulou I, Assimakopoulos SF and Triantos C were responsible for the drafting of the manuscript and the data interpretation; Assimakopoulos SF and Triantos C were responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

Conflict-of-interest statement: Not related to this article.

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: Christos Triantos, PhD, Assistant Professor in Internal Medicine and Gastroenterology, Department of Gastroenterology, University Hospital of Patras, D. Stamatopoulou 4, Patras 26504, Greece. chtriantos@upatras.gr
Telephone: +30-69-72894651
Fax: +30-26-10625382

Received: July 16, 2018

Peer-review started: July 16, 2018

First decision: July 31, 2018

Revised: August 2, 2018

Accepted: August 24, 2018

Article in press: August 24, 2018

Published online: September 28, 2018

Abstract

Considering that both innate and adaptive immune responses are involved in the pathogenesis of Crohn's disease (CD), novel therapeutic options have significantly been developed. Biological agents represent an important addition to the conventional treatments for immuno-inflammatory conditions, acting as antagonists of adhesion molecules or various inflammatory cytokines. The interleukin 12 (IL-12)/IL-23 common pathway has been found to play a determinant role in the induction of inflammation in adaptive immune responses. In particular, IL-23 promotes the differentiation of naïve T helper cells into Th17 phenotype with the concomitant secretion of several inflammatory cytokines such as IL-17 and IL-22, whereas IL-12 induces the Th1 polarization and production of critical cytokines such as interferon- γ and tumor necrosis factor. Nowadays, there is increased interest regarding the role of IL-23 as a therapeutic target of CD through the blockage of IL-23 mediated pathways. In this editorial, we focus on the role of IL-12/IL-23 pathway in the regulation of mucosal immunity and in the induction and maintenance of chronic inflammation. In parallel, we critically discuss the available data regarding the therapeutic effect of the IL-12/IL-23 inhibitors and especially of ustekinumab, a human monoclonal antibody which has been recently approved by the United States Food and Drug Administration for the management of moderate-to-severe CD and its potential to be used as first-line therapy in everyday clinical practice.

Key words: Crohn's disease; Interleukin 12; Interleukin

23; Monoclonal antibodies; Ustekinumab; Biological agents; Interleukin 12/interleukin 23 blockade

© **The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The therapeutic management of Crohn's disease patients not responding to treatment with anti-tumor necrosis factor agents remains a clinical challenge. Recently, there has been increased evidence regarding the development of new drugs with alternative mechanisms of action. Interleukin (IL)-12 and IL-23 are important cytokines which are involved in the adaptive immune responses and their common pathway has been found to play a determinant role in the induction of inflammation. Clinical trials have assessed the therapeutic effect of an IL-12/IL-23 inhibitor (ustekinumab), demonstrating rapid clinical effect with a safety profile. Further studies are needed to elucidate its potential role as first-line therapy in Crohn's disease.

Aggeletopoulou I, Assimakopoulos SF, Konstantakis C, Triantos C. Interleukin 12/interleukin 23 pathway: Biological basis and therapeutic effect in patients with Crohn's disease. *World J Gastroenterol* 2018; 24(36): 4093-4103 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i36/4093.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i36.4093>

INTRODUCTION

Crohn's disease (CD) is an immune-mediated inflammatory disorder characterized by chronic relapsing inflammation in different segments of the gastrointestinal tract. Although the typical preferential regions of involvement are the distal ileum, the ileocaecal region, the colon and the perianal region, extra-intestinal manifestations are not uncommon^[1]. The etiology of this disease is not yet fully understood. However, it is currently considered that genetic and environmental factors, impaired immune regulation, gut barrier dysfunction and changes in the intestinal microbiome are involved in the pathogenesis and development of this condition^[2-4]. CD treatment is generally individualized and is associated with several factors including disease phenotype, disease severity, affected region, and related luminal or extraluminal complications. The treatment strategy is mainly classified into two stages: (1) Appropriate treatment of the acute flare aiming to induce remission (2) maintenance of remission^[5]. Until recently, the initial choice of treatment has focused on long-term use of corticosteroids and immunosuppressants like thiopurines and methotrexate for the induction and the maintenance of remission, respectively^[6-8]. During the last years, therapeutic options have significantly benefited from the introduction of biological agents,

which became the mainstay of moderate to severe CD treatment, using monoclonal antibodies targeting tumor necrosis factor (TNF)^[9-11] or adhesion molecules (integrins)^[12,13]. However, a significant proportion of patients (about 30%) will not respond adequately to induction therapy with TNF inhibitors. Furthermore, another subgroup of patients that achieve initial (short-term) response, run a risk of secondary loss which occurs in approximately 40% of patients^[14,15]. The main causes of secondary failure are non-compliance to anti-TNF treatment, drug immunogenicity and non-immune clearance of anti-TNF or the persistence of inflammatory activity in spite of sufficient anti-TNF levels^[16]. This latter clinical scenario is usually performed by switching to another class of biological agents^[16]. Moreover, the humanized anti- $\alpha 4\beta 7$ integrin antibody that has been recently introduced in clinical practice, has displayed efficacy on the induction and maintenance of remission in moderate-to-severe refractory CD patients; however, safety concerns have been raised due to rare but possible adverse events^[17].

Current data suggest that the initiation and perpetuation of inflammation in CD are associated with a disruption in the balance among the intestinal epithelium, the commensal microbiota and the innate immune response^[18]. This condition is maintained by the presence of defects in the intestinal wall, environmental factors, genetic predisposition and dysfunction in regulatory mechanisms, which in turn lead to the release of an array of cytokines that promote the inflammatory immune response^[18].

Taking into consideration the adverse events resulted from previous treatments regimens, target tailored treatment options that aim at specific pathways of inflammation have emerged. CD is characterized by dysfunction in both innate and adaptive immune responses. Disturbances in adaptive immune response are closely related to tissue damage, mainly driven by interleukin (IL)-12 and IL-23^[4]. Therefore, inhibitors of IL-12/IL-23 and specific inhibitors of IL-23 have been developed for the management of CD. In this editorial, we focus on the role of IL-12/IL-23 pathway in the modulation of mucosal immunity and in the induction and maintenance of remission of the associated chronic inflammation of the intestinal epithelium. Moreover, we critically discuss the therapeutic effects of the IL-12/IL-23 blocker in patients with CD and its potential position as first-line therapy in everyday clinical practice.

IL-12 AND IL-23 ROLE IN CD/ MECHANISM OF ACTION

Both innate and adaptive immune responses are involved in the pathogenesis of CD. Adaptive immunity is provided by resident and recruited cells, including mucosal B cells which produce the secretory immunoglobulins A and G, T cells subpopulations and

especially T helper 1 (Th1), Th17, or Th2 cells, and T and B regulatory cells^[41]. Th1 phenotype is induced by microbes which in turn activate the excretion of interferon (IFN)- γ and IL-12p40 through the signal transducer and activator of transcription 1 (STAT1), T-box factor 21 (TBX21) and STAT4 signaling pathways^[19]. CD seems to be driven by a Th1-mediated pathology, with an increased synthesis of IFN- γ ^[20]. In parallel, inflamed intestinal mucosa is infiltrated by Th17 cells with a concomitant production of IL-17 cytokine^[21]. Th17 lineage commitment is directed by transforming growth factor beta (TGF- β) in the presence of a proinflammatory environment, and IL-23 is related to the expansion and maintenance of Th17 cells^[22]. Moreover, CD is characterized by an increased production of IL-12, the major Th1-stimulating factor^[23,24].

IL-12 family includes IL-12, IL-2, IL-35 and IL-27, key mediators of inflammatory response^[25]. IL-12 is a heterodimeric cytokine comprising of two covalently linked subunits (p40 and p35) and is mainly produced by activated phagocytic cells [monocytes/macrophages, neutrophils, dendritic cells (DCs)] in response to bacterial stimulation, intracellular pathogens and intestinal inflammation^[26,27]. IL-12 exerts its biological function through the binding to its heterodimeric receptor formed by IL-12R- β 1 and IL-12R- β 2. β 2 receptor subunit plays a major role in IL-12 function, as it controls the Th1 cell lineage commitment. Moreover, IL-12R- β 2 is overexpressed by T cells in inflamed mucosa^[26] as well as in CD T-lamina propria lymphocytes (T-LPL)^[28]. Data has shown that the inhibition of IL-12 resulted in reduced production of IFN- γ and IL-21 in CD mucosal T cells cultures^[23], and T cell stimulation in T cell cultures from fetal gut explants, promoting Th1 immune response and causing mucosal degradation^[29]. Beyond the role of IL-12 in T cells, a recent study has demonstrated its role in a distinct population, the innate lymphoid cells (ILCs), which are considerably encountered in inflamed tissue of intestinal wall of CD patients. IL-12 stimulates these cells to produce IFN- γ indicating the role of ILCs in the pathogenesis of gut mucosal inflammation^[30].

Recent studies have demonstrated the crucial role of IL-23 in the regulation of Th1 cell responses and its potential role in the CD pathogenesis. IL-23 belongs to the IL-12 family, it is composed of one subunit of p40, that is shared with IL12, and one subunit of p19, which is unique^[31]. IL-23 is produced by myeloid DCs or conventional DCs and macrophages in response to bacterial stimulation, endogenous signals or CD40L activation^[32,33]. Depending on the various environmental signals, macrophages can obtain distinct functional phenotypes through undergoing different polarization^[34]. Macrophage M1 phenotype is induced by microbial products or proinflammatory cytokines and is characterized by high production of IL-12 and IL-23 cytokines, in contrast to M2 phenotype which is mainly associated with Th2 immune responses and promotes tissue repair^[35]. The binding of IL-23 on its

receptor, which is composed of IL-12R β 1 and IL-23R results in the specific induction of naïve CD4⁺ T cells into Th17 cells, with a concomitant activation of numerous proinflammatory cytokines such as IL-17, IL-17F, TNF- α and IL-6^[36]. Beyond CD4⁺ T induction, IL-23 participates in the ILCs^[37], CD8⁺ T^[38], natural killer (NK), NKT^[39] and $\gamma\delta$ T cells^[40] activation. The presence of inflammation in the intestinal wall stems from the pathological Th1 immune response against the bacterial microbiota which are closely related to the IL-12 and IL-23 expression^[41]. IL-23 expression is highly increased in ILCs in the inflamed intestine in CD patients, indicating the presence of IL-23-responsive ILCs in the human gut and promoting IL-17A and IFN- γ production^[37,42]. Moreover, studies have demonstrated the existence of single nucleotide polymorphisms (SNPs) in the IL-23R gene, which are highly protective in CD patients, suggesting that the blockade of IL-23 signaling could decrease the risk of CD development^[43-45].

The above data highlighted the determinant role of IL-12 and IL-23 in intestinal inflammation, since they are able to trigger signals in different cell populations and lead to the introduction of monoclonal antibodies as therapeutic agents for CD, targeting the common p40 subunit of IL-12 and IL-23.

IL-12/IL-23 BLOCKADE/EMERGING BIOLOGICAL AGENTS

Anti-IL-12/IL-23p40 antibodies

Ustekinumab is an IgG1 humanized monoclonal antibody directed against the common p40 subunit of the IL-12 and IL-23. It binds to the p40 subunit and impedes the interaction with the IL-12R β 1 on the cell surface of NK, T cells, or antigen-presenting cells^[46]. This process results in the blockade of IL-12 and IL-23 mediated downstream cell signaling, gene activation and cytokine production^[46]. Ustekinumab binding to the IL-12 and IL-23, equally neutralizes IL-12 mediated responses, including the intracellular phosphorylation of STAT4, the expression of cell surface markers and the production of IFN- γ and IL-23 mediated responses including the intracellular phosphorylation of STAT3 and IL-17A, IL-17F, and the production of IL-22^[46] (Figure 1).

Briakinumab is an IgG1 monoclonal antibody with similar mechanism of action as ustekinumab, which was tested for the induction and maintenance of remission in patients with moderately to severely active CD. The results of a placebo-controlled phase 2b trial showed that although briakinumab presented a similar safety and tolerability profile to placebo in the induction and maintenance phases, it did not achieve the primary end point of clinical remission at week 6^[47].

Anti-IL-23p19 antibodies

MEDI2070 (or AMG 139) is a humanized monoclonal

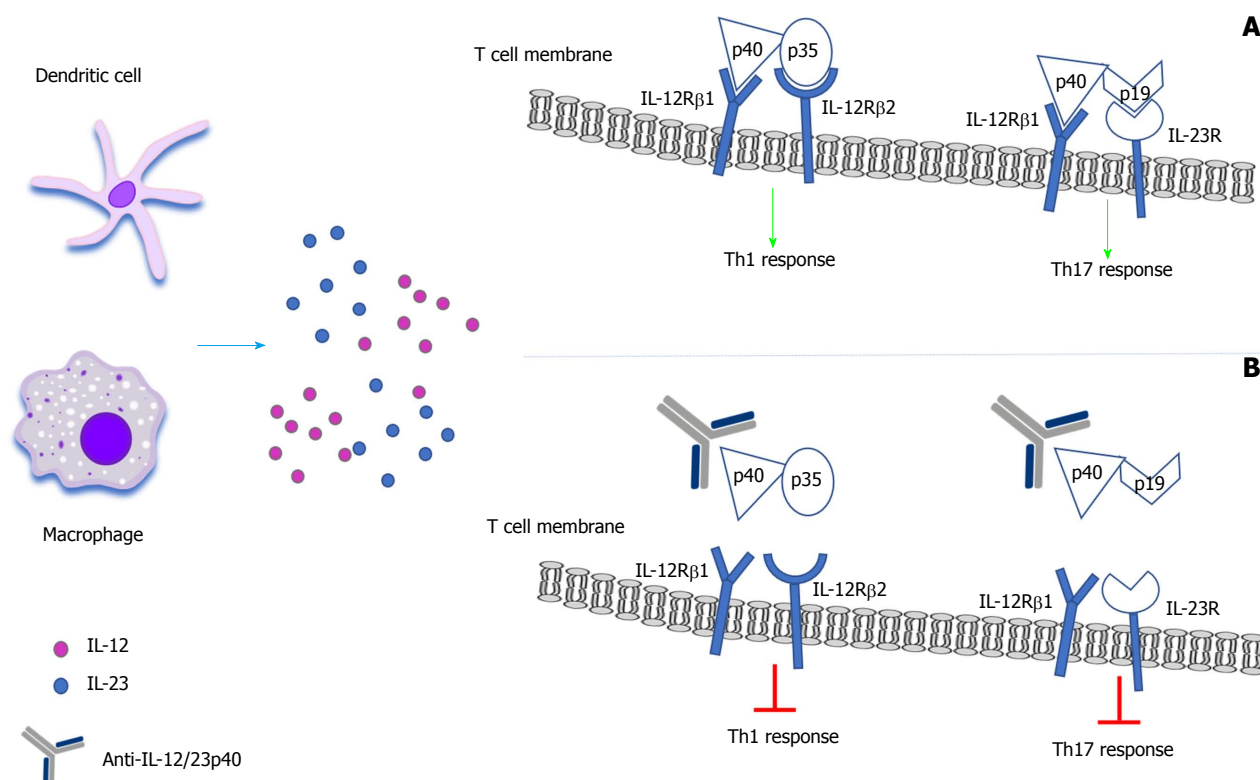


Figure 1 Neutralization of the interleukin-12/interleukin-23 pathways associated with T-cell activation and differentiation. A: In inflamed tissue, bacterial stimulation can lead to the activation of dendritic cells and macrophages. This process results in the activation of T cells and the secretion of inflammatory cytokines such as IL-12 and IL-23. The binding of IL-12 in its receptor, which is composed of IL-12R-β1 and IL-12R-β2 results in the preferential T cell differentiation into Th1 cells, promoting the Th1 cell response and secreting cytokines such as IFN-γ and TNF. The binding of IL-23 in its receptor, which is composed of IL-12R-β1 and IL-23R results in the preferential induction of T cells into Th17 cells, inducing Th17 cell response and secreting cytokines such as IL-17 and IL-22; B: The use of a monoclonal antibody against the common subunit of IL-12 and IL-23 (IL-12/23p40) that selectively targets both IL-23 and IL-12 cytokines, disrupts their mediated signaling pathway and cytokine cascade, through the prevention of these cytokines' interaction with their shared cell-surface receptor, IL-12R-β1. This process results in the inhibition of IL-12 and IL-23 signaling and further activation of Th1 and Th17 phenotypes. IL: Interleukin; IFN: Interferon; TNF: Tumor necrosis factor.

IgG2 antibody that selectively binds the p19 subunit, specifically blocking the binding of IL-23 to its receptor. In a phase 2a trial of patients with moderate to severe CD who had failed to anti-TNF treatment, the use of MEDI2070 showed induction of clinical response in CD patients compared to placebo^[48].

Risankizumab, a humanized monoclonal antibody targeting the p19 subunit of IL-23, resembles the mechanism of action of MEDI2070. The efficacy and safety of this antibody were assessed in a randomized, double-blind, placebo-controlled phase 2 study and the results showed that it was significantly better than placebo in inducing clinical remission^[49].

USTEKINUMAB

Ustekinumab was approved in 2017 by the United States Food and Drug Administration (FDA) for the treatment of moderate to severe active CD in patients who have failed or were intolerant to therapy with corticosteroids or other immunomodulators but have never failed anti-TNF treatment, or in patients who have failed or were intolerant to therapy with one or more anti-TNF agents^[50]. In parallel, in the same year, the use of

ustekinumab was approved by the European Medicines Agency (EMA) for adults with moderate to severe active CD with inadequate response, or loss of response, or intolerance to either conventional treatment, or anti-TNF agents, or with medical contraindications to such therapies^[51].

CLINICAL EFFICACY OF USTEKINUMAB IN CD/ RANDOMIZED CLINICAL TRIALS

The clinical efficacy of ustekinumab in humans was first evaluated in immune-mediated diseases, such as psoriasis^[52,53], psoriatic arthritis^[54-56] and multiple sclerosis^[57]. The current use of ustekinumab in patients with CD has been assessed by multiple clinical trials (Tables 1 and 2).

Phase II studies

The use of ustekinumab in the treatment of moderate to severe CD was first investigated in 2008 in a randomized, placebo-controlled, phase 2a induction trial^[58]. The study comprised of two patient groups. Population 1 (the double-blind, cross-over phase IIa arm of the study) included 104 patients who had previously

Table 1 Summary of randomized, placebo-controlled trials on ustekinumab in Crohn's disease

Study (reference)	Publication year	Type of publication	Study design	Study phase
Sandborn <i>et al</i> ^[58]	2008	Full paper	Multicenter, double-blind, placebo-controlled, parallel cross-over	IIa
Sandborn <i>et al</i> ^[59] (CERTIFI)	2012	Full paper	Randomized, multicenter, double-blind, placebo-controlled	IIb induction IIb maintenance
Feagan <i>et al</i> ^[60] (UNITI-1)	2016	Full paper	Randomized, multicenter, double-blind, placebo-controlled	III
Feagan <i>et al</i> ^[60] (UNITI-2)	2016	Full paper	Randomized, multicenter, double-blind, placebo-controlled	III
Feagan <i>et al</i> ^[60] (IM-UNITI)	2016	Full paper	Randomized, multicenter, double-blind, placebo-controlled	Maintenance phase of UNITI 1 and 2 responders
Sandborn <i>et al</i> ^[63] (IM-UNITI long term extension)	2017	Abstract	Randomized, multicenter, double-blind, placebo-controlled	Maintenance phase of UNITI 1 and 2 responders
Sands <i>et al</i> ^[62] (UNITI-IM)	2018	Abstract	Randomized, multicenter, double-blind, placebo-controlled	Maintenance phase of UNITI 1 and 2 responders
Rutgeerts <i>et al</i> ^[61]	2018	Full paper	Randomized, multicenter, double-blind, placebo-controlled	Induction and maintenance of endoscopic healing

received conventional therapy or anti-TNF regimens. The second group, population 2 - open-label arm, consisted of 27 non-responders (primary or secondary) to infliximab. The results showed that ustekinumab could induce clinical response in patients with moderate-to-severe active CD, especially in those who were previously treated with infliximab^[58]. Regarding the development of serious adverse events, there was no difference in patients receiving ustekinumab compared to placebo^[58]. The above results led to the conduct of a 36-wk, randomized, double-blind, placebo-controlled phase IIb trial (CERTIFI) on the role of ustekinumab in the induction and maintenance of remission in patients with moderate-to-severe CD who were resistant to anti-TNF treatment^[59]. The study enlisted 526 patients in the induction arm and 145 responders in the maintenance phase. The results demonstrated that patients who were resistant to anti-TNF therapy showed an increased response rate to induction with ustekinumab compared to placebo, although remission rates were comparable^[59]. However, ustekinumab induction responders showed significantly increased rates of response and remission during the maintenance phase^[59]. No difference was reported in the incidence of adverse events between examined groups during the maintenance phase^[59]. Basal-cell carcinoma developed in 1 patient receiving ustekinumab.

Phase III studies

Phase III, multicentre, double-blind, placebo-controlled, trials for the evaluation of ustekinumab in patients with moderate to severe CD have been recently completed. The first trial (UNITI-1) included 741 patients who were primary or secondary non-responders to anti-TNF treatment or had severe side effects^[60]. In the second trial (UNITI-2) 628 patients who had failed the conventional therapy or had experienced severe side effects were enrolled^[60]. The results showed that intravenous ustekinumab induced clinical response and

remission in patients from both trials (UNITI 1-2)^[60]. No difference in adverse and serious adverse events was reported between the groups. Moreover, there was no report of death, malignancy, opportunistic infections or tuberculosis in ustekinumab treated patients^[60]. The 397 patients who completed the induction trials (UNITI 1 and 2) and were responders to ustekinumab, were enrolled in the IM-UNITI trial^[60]. Primary endpoint for this trial was the maintenance of remission at week 44 and the results showed that treatment with ustekinumab was more effective than placebo for maintaining remission^[60]. Between the placebo and the ustekinumab groups, the rates of adverse events development and severity were similar^[60].

Effect of ustekinumab in endoscopic activity

A sub-study of the UNITI trial enrolled 334 patients with moderate to severe CD and assessed the clinical effect of ustekinumab in the simplified endoscopic activity score for CD (SES-CD) and the efficacy of maintenance therapy^[61]. Patients treated with ustekinumab had higher reduction in SES-CD compared to placebo during the induction phase^[61]. The results were similar in patients from different induction trials (UNITI 1 or 2) and in those receiving different ustekinumab doses. Greater reduction in the SES-CD at week 44 was also observed in the ustekinumab group compared to placebo^[61].

Dose adjustment effect of ustekinumab in patients with loss of response or in delayed responders

Another sub-study of the UNITI-IM maintenance programme addressed important points of clinical application of ustekinumab. This trial evaluated the clinical effect of dose adjustment of ustekinumab in patients who (1) entered the maintenance trial in response and subsequently lost response (LOR) (2) were non-responders to intravenous ustekinumab during induction phase^[62]. The results showed that in patients

Table 2 Characteristics of randomized, placebo-controlled trials evaluating the efficacy of ustekinumab in Crohn's disease

Study (reference)	Patients	Endpoints	Intervention parameters	Outcomes
Sandborn <i>et al</i> ^[58]	25	Clinical response at week	90 mg SC week 0-3→Placebo SC week 8-11	Ustekinumab:
	26	4/week 8	Placebo SC week 0-3→90mg SC week 8-11	53%/49%
	26		4.5 mg/Kg IV week 0→Placebo IV week 8	Placebo:
	27		Placebo IV week 0→4.5 mg/Kg IV week 8	30%/40%
Sandborn <i>et al</i> ^[59] (CERTIFI)	27 (primary or secondary non-responders to infliximab)	Clinical response at week 8	90 mg SC	43%
			4.5 mg/kg IV	54%
	131	Clinical response at week 6	1 mg/kg IV	36.60%
	132		3 mg/kg IV	34.10%
Induction	131		6 mg/kg IV	39.70%
	132		Placebo IV	23.50%
	145 Responders	Clinical response at week 22	90 mg SC	69.40%
	72 Ustekinumab		Placebo SC	42.50%
Sandborn <i>et al</i> ^[59] (CERTIFI) Maintenance	73 Placebo	Clinical remission at week 22	90 mg SC	41.70%
			Placebo SC	27.40%
			130 mg IV	34.30%
			6 mg/kg IV	33.70%
Feagan <i>et al</i> ^[60] UNITI-1 induction	245	Clinical response at week 6	Placebo IV	21.50%
	249		130 mg IV	51.70%
	247		6 mg/kg IV	55.50%
			Placebo IV	28.70%
Feagan <i>et al</i> ^[60] UNITI-2 induction	209	Clinical response at week 6	130 mg IV	51.70%
	209		6 mg/kg IV	55.50%
	210		Placebo IV	28.70%
Feagan <i>et al</i> ^[60] IM- UNITI maintenance	132	Clinical remission at week 44	90 mg SC every 8 wk	53.10%
	132		90 mg SC every 12 wk	48.80%
	133		Placebo SC	35.90%
Sandborn <i>et al</i> ^[63] (IM- UNITI long term extension)	1281	Clinical remission at week 92	90 mg SC every 8 wk	74.40%
			90 mg SC every 12 wk	72.60%
			Subjects with prior dose adjustment	53.50%
			All ustekinumab treated	67.50%
Sands <i>et al</i> ^[62] (IM-UNITI patients with dose adjustment following loss of response)	51	Clinical response [CR-100] ¹	Placebo to 90 mg SC ustekinumab every 8 wk	71%
	29		Ustekinumab 90 mg SC every 12 wk to ustekinumab 90 mg SC every 8 wk	55%
	28		No dose adjustment	46%
			Additional dose of 90 mg SC	50.50%
Sands <i>et al</i> ^[62] (IM-UNITI non-responders during induction phase having an additional SC dose)	467	Clinical response 8 wk after one additional dose		
		Clinical remission 8 wk after one additional dose		28.90%
Rutgeerts <i>et al</i> ^[61] Induction week 8	155	SES-CD Change from baseline, mean (SD)	130 mg IV/6 mg/kg	-2.8 (8.10) ^a
	97		Placebo IV	-0.7 (4.97)
	47	SES-CD Change from baseline, mean (SD)	90mg SC every 12 wk	-1.5 (4.22)
	74		90mg SC every 8 wk	-3.8 (6.02)
Rutgeerts <i>et al</i> ^[61] Maintenance week 44	51		Placebo SC	-2.0 (5.35)

¹CR-100, ≥ 100-point decrease in Crohn's Disease Activity Index; ^aP < 0.05. SC: Subcutaneous; IV: Intravenous; SES-CD: Simplified endoscopic activity score for Crohn's disease; SD: Standard deviation.

with LOR, the dose adjustment of ustekinumab (12-wk interval to 8-wk interval) provided clinical benefits compared to patients who remained to the 8-wk interval. Moreover, patients who were initial non-responders to induction treatment benefited from continued treatment (at least 1 additional subcutaneous dose) following the initial intravenous dose (rescue therapy - late responders)^[62].

Long-term efficacy and safety of ustekinumab

The long-term efficacy and safety of ustekinumab were evaluated in an ongoing IM-UNITI study with a duration of approximately 5 years^[63]. The preliminary results through week 96 showed that the clinical response and remission were maintained in patients who were under treatment with subcutaneous ustekinumab. There was no difference in adverse events and infection rates

between patients treated with ustekinumab or placebo from week 44 through week 96^[63].

DISCUSSION

The introduction of monoclonal antibodies in the last decades has changed the therapeutic strategy of CD. The biological factors that have been approved to date for the management of CD include anti-TNF agents (adalimumab, certolizumab and infliximab), anti-integrins (natalizumab and vedolizumab) and the anti-IL-12/IL-23p40 agent (ustekinumab). The clinical benefits of monoclonal antibodies are the efficacy and safety during the induction and maintenance of clinical response as well as a decreased risk of hospitalization and surgery. Anti-TNF agents are currently positioned as first line biologic treatment for the management of

moderate to severe CD and have been proven to be effective for both induction and maintenance of CD patients^[64]. However, these agents do not fully cover the needs of all patients as there is significant percentage who was not respond to treatment, or even if they achieved an initial short-term response, they could undergo secondary failure to anti-TNF agents or develop unacceptable adverse events, which lead to treatment discontinuation. Currently, for patients with primary failure to anti-TNF treatment, the use of a second TNF agonist is not indicated and a switch to another agent with a different mechanism of action is suggested^[65,66]. The anti- $\alpha 4\beta 7$ integrin antibody was approved for induction and maintenance of CD patients, but due to its fairly slow-action, it is considered better for the maintenance phase.

Clinical evidence suggests that ustekinumab may be preferred over the anti-integrin treatment given its rapid onset of action^[60]. In particular, the clinical benefits of ustekinumab over vedolizumab in inducing clinical response and remission have been shown in patients who were non-responders or were intolerant to anti-TNF treatment, since ustekinumab treated patients responded as early as week 3^[60] compared to patients treated with vedolizumab who responded at week 10^[67]. The results of the study IM-UNITI LTE have shown that the rapid onset of ustekinumab action is accompanied by a long duration of action, as 75% of patients in remission at year 1, were still in remission at year 2, indicating one more advantage over the anti-TNF or anti-integrins agents^[63].

The route of ustekinumab administration could be considered as an important benefit over the other treatment options. During induction phase, only one intravenous dose of ustekinumab is required for the development of clinical response and during maintenance phase, a single subcutaneous dose is able to induce clinical response up to 44 wk in one-third of the patients^[60]. These results highlight the usefulness of ustekinumab as a more convenient option with its potential for a home-based therapy. Moreover, a sub-study of the IM-UNITI programme has shown that ustekinumab dose adjustment can provide additional clinical advantage in patients with loss of response. The results demonstrated that initial non-responders to the induction therapy could benefit more from continued treatment with at least one additional dose^[62].

The study by Fegan *et al.*^[60], has shown that the rapid onset of clinical efficacy was accompanied by a reduction in CRP and fecal calprotectin levels which persisted during the maintenance phase up to week 44. The improvement in CRP and fecal calprotectin levels following ustekinumab treatment suggests that decrease of inflammation occurred along with the clinical improvement^[60]. In parallel, recent data has demonstrated the ability of ustekinumab to induce endoscopic healing during the induction phase (at week

8) in patients with moderate to severe CD^[61].

Beyond the obvious benefits of ustekinumab in the management of moderate to severe CD, patient safety is an important factor of determining the risk/benefit ratio of each treatment option. Although the data from studies evaluating the long-term safety of ustekinumab in patients with moderate to severe psoriasis and multiple sclerosis suggests an increased risk of serious infections, in CD patients the drug seems to have a rather favorable safety profile^[58-60,63], which is very important considering the role of IL-12/IL-23 in maintaining immune homeostasis^[68-71].

Taking into consideration the above advantages, we can speculate the use of ustekinumab as a first-line treatment or its use in conjunction with or before other biological agents, following corticosteroid failure. Ustekinumab may be the ideal option for frail patients, considering its safety profile and the mode of administration. In addition, CD patients with other immune mediated diseases such as previous history of multiple sclerosis and psoriasis or patients with TNF agonist induced psoriasis represent promising candidates for ustekinumab treatment considering its systemic anti-inflammatory action^[52-56,72,73]. On the other hand, the use of ustekinumab may not be favored in patients with perianal fistulizing CD in whom the use of infliximab is proposed^[74]. Furthermore, there is limited evidence concerning the use of ustekinumab in pregnancy and breast feeding. Studies in animals have shown no developmental toxicity due to ustekinumab exposure^[75]. In humans, there are two case reports of abortions in ustekinumab-exposed pregnancies^[76,77] and two successful pregnancies after prolonged ustekinumab treatment^[78,79].

CONCLUSION

Ustekinumab has exhibited considerable potential in the management of intestinal inflammation by downregulating the immune system through its binding in the common subunit of IL-12 and IL-23 and by blocking their action. In light of current evidence, ustekinumab is considered to be an effective drug with a favorable safety profile for the management of patients with moderate-to-severe active CD. Its use appears to be very promising in patients with an inadequate response, loss of response, intolerance or contraindications to treatment with traditional anti-TNF agents. Moreover, ustekinumab could be considered as first line biological treatment in patients who failed conventional therapy, although the high treatment cost poses severe limitations to this alternative. Large scale-multicentre trials with long term follow up and high-quality evidence are required to further explore the spot that this novel agent should hold in the CD treatment algorithms, and its role in specific disease phenotypes (such as fistulizing disease, early-onset

CD or postoperative setting). Lastly, conduct of head-to-head comparison studies of ustekinumab with other biological agents, evaluation of drug to drug interactions and pharmacoeconomic (cost effective) analysis of ustekinumab are the next steps towards thoroughly delineating the place of ustekinumab in clinical practice.

REFERENCES

- Freeman HJ. Natural history and long-term clinical course of Crohn's disease. *World J Gastroenterol* 2014; **20**: 31-36 [PMID: 24415855 DOI: 10.3748/wjg.v20.i1.31]
- Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011; **140**: 1785-1794 [PMID: 21530745 DOI: 10.1053/j.gastro.2011.01.055]
- Liu TC, Stappenbeck TS. Genetics and Pathogenesis of Inflammatory Bowel Disease. *Annu Rev Pathol* 2016; **11**: 127-148 [PMID: 26907531 DOI: 10.1146/annurev-pathol-012615-044152]
- Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; **448**: 427-434 [PMID: 17653185 DOI: 10.1038/nature06005]
- Raad MA, Chams NH, Sharara AI. New and Evolving Immunotherapy in Inflammatory Bowel Disease. *Inflamm Intest Dis* 2016; **1**: 85-95 [PMID: 29922662 DOI: 10.1159/000445986]
- Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012; **380**: 1590-1605 [PMID: 22914295 DOI: 10.1016/S0140-6736(12)60026-9]
- Feagan BG, Rochon J, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Gillies R, Hopkins M. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995; **332**: 292-297 [PMID: 7816064 DOI: 10.1056/nejm199502023320503]
- Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980; **302**: 981-987 [PMID: 6102739 DOI: 10.1056/nejm198005013021801]
- 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]
- Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962 DOI: 10.1016/S0140-6736(02)08512-4]
- Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, Schreiber S; PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007; **357**: 228-238 [PMID: 17634458 DOI: 10.1056/NEJMoa067594]
- Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369**: 711-721 [PMID: 23964933 DOI: 10.1056/NEJMoa1215739]
- Vermeire S, Loftus EV Jr, Colombel JF, Feagan BG, Sandborn WJ, Sands BE, Danese S, D'Haens GR, Kaser A, Panaccione R, Rubin DT, Shafran I, McAuliffe M, Kaviya A, Sankoh S, Mody R, Abhyankar B, Smyth M. Long-term Efficacy of Vedolizumab for Crohn's Disease. *J Crohns Colitis* 2017; **11**: 412-424 [PMID: 27683798 DOI: 10.1093/ecco-jcc/jjw176]
- Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, Kuenzig E, Tomlinson G, Siegel CA, Melmed GY, Kaplan GG. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology* 2015; **148**: 344-354.e5; quiz e14-e15 [PMID: 25448924 DOI: 10.1053/j.gastro.2014.10.011]
- Danese S, Fiorino G, Reinisch W. Review article: Causative factors and the clinical management of patients with Crohn's disease who lose response to anti-TNF- α therapy. *Aliment Pharmacol Ther* 2011; **34**: 1-10 [PMID: 21539588 DOI: 10.1111/j.1365-2036.2011.04679.x]
- Ding NS, Hart A, De Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease - algorithm for practical management. *Aliment Pharmacol Ther* 2016; **43**: 30-51 [PMID: 26515897 DOI: 10.1111/apt.13445]
- Pagnini C, Arseneau KO, Cominelli F. Natalizumab in the treatment of Crohn's disease patients. *Expert Opin Biol Ther* 2017; **17**: 1433-1438 [PMID: 28832222 DOI: 10.1080/14712598.2017.1366444]
- Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. *Annu Rev Immunol* 2010; **28**: 573-621 [PMID: 20192811 DOI: 10.1146/annurev-immunol-030409-101225]
- Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 2007; **25**: 821-852 [PMID: 17201677 DOI: 10.1146/annurev.immunol.25.022106.141557]
- Neurath MF, Weigmann B, Finotto S, Glickman J, Nieuwenhuis E, Iijima H, Mizoguchi A, Mizoguchi E, Mudter J, Galle PR, Bhan A, Autschbach F, Sullivan BM, Szabo SJ, Glimcher LH, Blumberg RS. The transcription factor T-bet regulates mucosal T cell activation in experimental colitis and Crohn's disease. *J Exp Med* 2002; **195**: 1129-1143 [PMID: 11994418 DOI: 10.1084/jem.20011956]
- Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, Bamba T, Fujiyama Y. Increased expression of interleukin 17 in inflammatory bowel disease. *Gut* 2003; **52**: 65-70 [PMID: 12477762]
- Bettelli E, Oukka M, Kuchroo VK. T(H)-17 cells in the circle of immunity and autoimmunity. *Nat Immunol* 2007; **8**: 345-350 [PMID: 17375096 DOI: 10.1038/ni0407-345]
- Monteleone G, Biancone L, Marasco R, Morrone G, Marasco O, Luzzza F, Pallone F. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology* 1997; **112**: 1169-1178 [PMID: 9098000 DOI: 10.1016/S0016-5085(97)70128-8]
- Parronchi P, Romagnani P, Annunziato F, Sampaio G, Beccio A, Giannarini L, Maggi E, Pupilli C, Tonelli F, Romagnani S. Type 1 T-helper cell predominance and interleukin-12 expression in the gut of patients with Crohn's disease. *Am J Pathol* 1997; **150**: 823-832 [PMID: 9060820]
- Gee K, Guzzo C, Che Mat NF, Ma W, Kumar A. The IL-12 family of cytokines in infection, inflammation and autoimmune disorders. *Inflamm Allergy Drug Targets* 2009; **8**: 40-52 [PMID: 19275692 DOI: 10.2174/187152809787582507]
- Trinchieri G. Interleukin-12: a cytokine produced by antigen-presenting cells with immunoregulatory functions in the generation of T-helper cells type 1 and cytotoxic lymphocytes. *Blood* 1994; **84**: 4008-4027 [PMID: 7994020 DOI: 10.1017/CBO9781107415324.004]
- Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nat Rev Immunol* 2003; **3**: 133-146 [PMID: 12563297 DOI: 10.1038/nri1001]
- Parrello T, Monteleone G, Cucchiara S, Monteleone I, Sebkova L, Doldo P, Luzzza F, Pallone F. Up-regulation of the IL-12 receptor beta 2 chain in Crohn's disease. *J Immunol* 2000; **165**: 7234-7239 [PMID: 11120856 DOI: 10.4049/jimmunol.165.12.7234]
- Monteleone G, MacDonald TT, Wathen NC, Pallone F, Pender SL. Enhancing Lamina propria Th1 cell responses with interleukin 12

- produces severe tissue injury. *Gastroenterology* 1999; **117**: 1069-1077 [PMID: 10535869 DOI: 10.1016/S0016-5085(99)70391-4]
- 30 **Bernink JH**, Peters CP, Munneke M, te Velde AA, Meijer SL, Weijer K, Hreggvidsdottir HS, Heinsbroek SE, Legrand N, Buskens CJ, Bemelman WA, Mjösberg JM, Spits H. Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. *Nat Immunol* 2013; **14**: 221-229 [PMID: 23334791 DOI: 10.1038/ni.2534]
- 31 **Hunter CA**. New IL-12-family members: IL-23 and IL-27, cytokines with divergent functions. *Nat Rev Immunol* 2005; **5**: 521-531 [PMID: 1599093 DOI: 10.1038/nri1648]
- 32 **Vignali DA**, Kuchroo VK. IL-12 family cytokines: immunological playmakers. *Nat Immunol* 2012; **13**: 722-728 [PMID: 22814351 DOI: 10.1038/ni.2366]
- 33 **Lyakh L**, Trinchieri G, Provezza L, Carra G, Gerosa F. Regulation of interleukin-12/interleukin-23 production and the T-helper 17 response in humans. *Immunol Rev* 2008; **226**: 112-131 [PMID: 19161420 DOI: 10.1111/j.1600-065X.2008.00700.x]
- 34 **O'Shea JJ**, Paul WE. Mechanisms underlying lineage commitment and plasticity of helper CD4+ T cells. *Science* 2010; **327**: 1098-1102 [PMID: 20185720 DOI: 10.1126/science.1178334]
- 35 **Martinez FO**, Helming L, Gordon S. Alternative activation of macrophages: an immunologic functional perspective. *Annu Rev Immunol* 2009; **27**: 451-483 [PMID: 19105661 DOI: 10.1146/annurev.immunol.021908.132532]
- 36 **Iwakura Y**, Ishigame H. The IL-23/IL-17 axis in inflammation. *J Clin Invest* 2006; **116**: 1218-1222 [PMID: 16670765 DOI: 10.1172/jci28508]
- 37 **Geremia A**, Arancibia-Cárcamo CV, Fleming MP, Rust N, Singh B, Mortensen NJ, Travis SP, Powrie F. IL-23-responsive innate lymphoid cells are increased in inflammatory bowel disease. *J Exp Med* 2011; **208**: 1127-1133 [PMID: 21576383 DOI: 10.1084/jem.20101712]
- 38 **Vanden Eijnden S**, Gorieli S, De Wit D, Willems F, Goldman M. IL-23 up-regulates IL-10 and induces IL-17 synthesis by polyclonally activated naive T cells in human. *Eur J Immunol* 2005; **35**: 469-475 [PMID: 15682457 DOI: 10.1002/eji.200425677]
- 39 **van de Wetering D**, de Paus RA, van Dissel JT, van de Vosse E. IL-23 modulates CD56+ /CD3- NK cell and CD56+ /CD3+ NK-like T cell function differentially from IL-12. *Int Immunol* 2009; **21**: 145-153 [PMID: 19088061 DOI: 10.1093/intimm/dxn132]
- 40 **Ness-Schwickerath KJ**, Jin C, Morita CT. Cytokine requirements for the differentiation and expansion of IL-17A- and IL-22-producing human Vgamma2Vdelta2 T cells. *J Immunol* 2010; **184**: 7268-7280 [PMID: 20483730 DOI: 10.4049/jimmunol.1000600]
- 41 **Hue S**, Ahern P, Buonocore S, Kullberg MC, Cua DJ, McKenzie BS, Powrie F, Maloy KJ. Interleukin-23 drives innate and T cell-mediated intestinal inflammation. *J Exp Med* 2006; **203**: 2473-2483 [PMID: 17030949 DOI: 10.1084/jem.20061099]
- 42 **Buonocore S**, Ahern PP, Uhlig HH, Ivanov IL, Littman DR, Maloy KJ, Powrie F. Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. *Nature* 2010; **464**: 1371-1375 [PMID: 20393462 DOI: 10.1038/nature08949]
- 43 **Duerr RH**, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO, Schumm LP, Lee AT, Gregersen PK, Barnada MM, Rotter JI, Nicolae DL, Cho JH. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006; **314**: 1461-1463 [PMID: 17068223 DOI: 10.1126/science.1135245]
- 44 **Pidasheva S**, Trifari S, Phillips A, Hackney JA, Ma Y, Smith A, Sohn SJ, Spits H, Little RD, Behrens TW, Honigberg L, Ghilardi N, Clark HF. Functional studies on the IBD susceptibility gene IL23R implicate reduced receptor function in the protective genetic variant R381Q. *PLoS One* 2011; **6**: e25038 [PMID: 22022372 DOI: 10.1371/journal.pone.0025038]
- 45 **Van Limbergen J**, Wilson DC, Satsangi J. The genetics of Crohn's disease. *Annu Rev Genomics Hum Genet* 2009; **10**: 89-116 [PMID: 19453248 DOI: 10.1146/annurev-genom-082908-150013]
- 46 **Benson JM**, Peritt D, Scallan BJ, Heavner GA, Shealy DJ, Giles-Komar JM, Mascelli MA. Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders. *MAbs* 2011; **3**: 535-545 [PMID: 22123062 DOI: 10.4161/mabs.3.6.17815]
- 47 **Panaccione R**, Sandborn WJ, Gordon GL, Lee SD, Safdi A, Sedghi S, Feagan BG, Hanauer S, Reinisch W, Valentine JF, Huang B, Carcereri R. Briakinumab for treatment of Crohn's disease: results of a randomized trial. *Inflamm Bowel Dis* 2015; **21**: 1329-1340 [PMID: 25989338 DOI: 10.1097/MIB.0000000000000366]
- 48 **Sands BE**, Chen J, Feagan BG, Penney M, Rees WA, Danese S, Higgins PDR, Newbold P, Faggioni R, Patra K, Li J, Klekotka P, Morehouse C, Pulkstenis E, Drappa J, van der Merwe R, Gasser RA Jr. Efficacy and Safety of MEDI2070, an Antibody Against Interleukin 23, in Patients With Moderate to Severe Crohn's Disease: A Phase 2a Study. *Gastroenterology* 2017; **153**: 77-86.e6 [PMID: 28390867 DOI: 10.1053/j.gastro.2017.03.049]
- 49 **Feagan BG**, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, Louis E, Franchimont D, Dewit O, Seidler U, Kim KJ, Neurath MF, Schreiber S, Scholl P, Pamulapati C, Lalovic B, Visvanathan S, Padula SJ, Herichova I, Soaita A, Hall DB, Böcher WO. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet* 2017; **389**: 1699-1709 [PMID: 28411872 DOI: 10.1016/S0140-6736(17)30570-6]
- 50 FDA approves STELARA® (Ustekinumab) for treatment of moderate to severe Crohn's disease. New York, CCFA, 2016. Available from: URL: <http://www.ccfa.org/news/Stelara.html>
- 51 European Commission approves Stelara® (Ustekinumab) for treatment of adults with moderately to severely active Crohn's disease. Beerse, Belgium: Johnson Johnson Media Center, 2016. Available from: URL: <https://www.jnj.com/media-center/press-releases/european-commission-approves-stelara-ustekinumab-for-treatment-of-adults-with-moderately-to-severely-active-crohns-disease>
- 52 **Leonardi CL**, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB; PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; **371**: 1665-1674 [PMID: 18486739 DOI: 10.1016/S0140-6736(08)60725-4]
- 53 **Papp KA**, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu MC, Wang Y, Li S, Dooley LT, Reich K; PHOENIX 2 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371**: 1675-1684 [PMID: 18486740 DOI: 10.1016/S0140-6736(08)60726-6]
- 54 **Gottlieb A**, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, Fretzin S, Kunyetz R, Kavanaugh A. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009; **373**: 633-640 [PMID: 19217154 DOI: 10.1016/S0140-6736(09)60140-9]
- 55 **McInnes IB**, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, Brodmerkel C, Li S, Wang Y, Mendelsohn AM, Doyle MK; PSUMMIT 1 Study Group. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013; **382**: 780-789 [PMID: 23769296 DOI: 10.1016/S0140-6736(13)60594-2]
- 56 **Ritchlin C**, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, Wang Y, Shen YK, Doyle MK, Mendelsohn AM, Gottlieb AB; PSUMMIT 2 Study Group. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in

- patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-mo and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 2014; **73**: 990-999 [PMID: 24482301 DOI: 10.1136/annrheumdis-2013-204655]
- 57 **Segal BM**, Constantinescu CS, Raychaudhuri A, Kim L, Fidelus-Gort R, Kasper LH; Ustekinumab MS Investigators. Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study. *Lancet Neurol* 2008; **7**: 796-804 [PMID: 18703004 DOI: 10.1016/S1474-4422(08)70173-X]
- 58 **Sandborn WJ**, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, Johanns J, Blank M, Rutgeerts P; Ustekinumab Crohn's Disease Study Group. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008; **135**: 1130-1141 [PMID: 18706417 DOI: 10.1053/j.gastro.2008.07.014]
- 59 **Sandborn WJ**, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, Ghosh S, de Villiers WJ, Panaccione R, Greenberg G, Schreiber S, Lichtiger S, Feagan BG; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012; **367**: 1519-1528 [PMID: 23075178 DOI: 10.1056/NEJMoa1203572]
- 60 **Feagan BG**, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johanns J, Gao LL, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel JF, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EV Jr, Dieleman LA, Katz S, Rutgeerts P; UNITI-IM-UNITI Study Group. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med* 2016; **375**: 1946-1960 [PMID: 27959607 DOI: 10.1056/NEJMoa1602773]
- 61 **Rutgeerts P**, Gasink C, Chan D, Lang Y, Pollack P, Colombel JF, Wolf DC, Jacobstein D, Johanns J, Szapary P, Adedokun OJ, Feagan BG, Sandborn WJ. Efficacy of Ustekinumab in Inducing Endoscopic Healing in Patients with Crohn's Disease. *Gastroenterology* 2018 [PMID: 29909019 DOI: 10.1053/j.gastro.2018.06.035]
- 62 **Sands B**, Gasink C, Jacobstein D, Gao L, Johanns J, Szapary P, Colombel J, Targan S, Ghosh S, Sandborn W. A85 Efficacy and safety of dose adjustment and delayed response to ustekinumab in moderate-severe Crohn's disease patients: results from the IM-UNIT maintenance study. *Can J Gastroenterol Hepatol* 2018; **1** Suppl 1: 147-148
- 63 **Sandborn W**, Rutgeerts P, Gasink C, Jacobstein D, Gao L-L, Johanns J, Sands B, Hanauer S, Targan S, Ghosh S. OP010 Long term efficacy and safety of Ustekinumab for Crohn's disease: results from IM-UNITI long-term extension through 2 years. *J Crohns Colitis* 2017; **11** Suppl 1: S6-S6
- 64 **Terdiman JP**, Gruss CB, Heidelbaugh JJ, Sultan S, Falck-Ytter YT; AGA Institute Clinical Practice and Quality Management Committee. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF- α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology* 2013; **145**: 1459-1463 [PMID: 24267474 DOI: 10.1053/j.gastro.2013.10.047]
- 65 **Gisbert JP**, Marin AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther* 2015; **41**: 613-623 [PMID: 25652884 DOI: 10.1111/apt.13083]
- 66 **Armuzzi A**, Gionchetti P, Daperno M, Danese S, Orlando A, Lia Scribano M, Vecchi M, Rizzello F; GIVI (Gruppo Italiano su Vedolizumab nelle IBD) Group. Expert consensus paper on the use of Vedolizumab for the management of patients with moderate-to-severe Inflammatory Bowel Disease. *Dig Liver Dis* 2016; **48**: 360-370 [PMID: 26821929 DOI: 10.1016/j.dld.2015.12.016]
- 67 **Sands BE**, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, D'Haens G, Ben-Horin S, Xu J, Rosario M, Fox I, Parikh A, Milch C, Hanauer S. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014; **147**: 618-627. e3 [PMID: 24859203 DOI: 10.1053/j.gastro.2014.05.008]
- 68 **Dávila-Seijo P**, Dauden E, Descalzo MA, Carretero G, Carrascosa JM, Vanaclocha F, Gómez-García FJ, De la Cueva-Dobao P, Herrera-Ceballos E, Belinchón I, López-Esteban JL, Alsina M, Sánchez-Carazo JL, Ferrán M, Torrado R, Ferrandiz C, Rivera R, Llamas M, Jiménez-Puya R, García-Doval I; BIOBADADERM Study Group. Infections in Moderate to Severe Psoriasis Patients Treated with Biological Drugs Compared to Classic Systemic Drugs: Findings from the BIOBADADERM Registry. *J Invest Dermatol* 2017; **137**: 313-321 [PMID: 27677836 DOI: 10.1016/j.jid.2016.08.034]
- 69 **Fiorantino D**, Ho V, Lebwohl MG, Leite L, Hopkins L, Galindo C, Goyal K, Langholff W, Fakharzadeh S, Srivastava B, Langley RG. Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry. *J Am Acad Dermatol* 2017; **77**: 845-854.e5 [PMID: 28893407 DOI: 10.1016/j.jaad.2017.07.013]
- 70 **Papp K**, Gottlieb AB, Naldi L, Pariser D, Ho V, Goyal K, Fakharzadeh S, Chevrier M, Calabro S, Langholff W, Krueger G. Safety Surveillance for Ustekinumab and Other Psoriasis Treatments From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Drugs Dermatol* 2015; **14**: 706-714 [PMID: 26151787]
- 71 **Singh S**, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. *Aliment Pharmacol Ther* 2018 [PMID: 29920733 DOI: 10.1111/apt.14852]
- 72 **Tillack C**, Ehmann LM, Friedrich M, Laubender RP, Papay P, Vogelsang H, Stallhofer J, Beigel F, Bedynek A, Wetzke M, Maier H, Koburger M, Wagner J, Glas J, Diegelmann J, Koglin S, Dombrowski Y, Schaubert J, Wollenberg A, Brand S. Anti-TNF antibody-induced psoriasisiform skin lesions in patients with inflammatory bowel disease are characterised by interferon- γ -expressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. *Gut* 2014; **63**: 567-577 [PMID: 23468464 DOI: 10.1136/gutjnl-2012-302853]
- 73 **Wils P**, Bouhnik Y, Michetti P, Flourie B, Brixi H, Bourrier A, Allez M, Duclos B, Grimaud JC, Buisson A, Amiot A, Fumery M, Roblin X, Peyrin-Biroulet L, Filippi J, Bouguen G, Abitbol V, Coffin B, Simon M, Laharie D, Pariente B; Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif. Subcutaneous Ustekinumab Provides Clinical Benefit for Two-Thirds of Patients With Crohn's Disease Refractory to Anti-Tumor Necrosis Factor Agents. *Clin Gastroenterol Hepatol* 2016; **14**: 242-50.e1-2 [PMID: 26432476 DOI: 10.1016/j.cgh.2015.09.018]
- 74 **Lee MJ**, Parker CE, Taylor SR, Guizzetti L, Feagan BG, Lobo AJ, Jairath V. Efficacy of Medical Therapies for Fistulizing Crohn's Disease: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018 [PMID: 29374617 DOI: 10.1016/j.cgh.2018.01.030]
- 75 **Martin PL**, Sachs C, Imai N, Tsusaki H, Oneda S, Jiao Q, Treacy G. Development in the cynomolgus macaque following administration of ustekinumab, a human anti-IL-12/23p40 monoclonal antibody, during pregnancy and lactation. *Birth Defects Res B Dev Reprod Toxicol* 2010; **89**: 351-363 [PMID: 20540088 DOI: 10.1002/bdrb.20250]
- 76 **Fotiadou C**, Lazaridou E, Sotiriou E, Ioannides D. Spontaneous abortion during ustekinumab therapy. *J Dermatol Case Rep* 2012; **6**: 105-107 [PMID: 23329988 DOI: 10.3315/jder.2012.1116]
- 77 **Venturin C**, Nancey S, Danion P, Uzzan M, Chauvenet M, Bergoin C, Roblin X, Flourie B, Boschetti G. Fetal death in utero and miscarriage in a patient with Crohn's disease under therapy with ustekinumab: case-report and review of the literature. *BMC Gastroenterol* 2017; **17**: 80 [PMID: 28629323 DOI: 10.1186/s12876-017-0633-6]

- 78 **Cortes X**, Borrás-Blasco J, Antequera B, Fernandez-Martinez S, Casterá E, Martin S, Molés JR. Ustekinumab therapy for Crohn's disease during pregnancy: a case report and review of the literature. *J Clin Pharm Ther* 2017; **42**: 234-236 [PMID: 28004853 DOI: 10.1111/jcpt.12492]
- 79 **Galli-Novak E**, Mook SC, Büning J, Schmidt E, Zillikens D, Thaci D, Ludwig RJ. Successful pregnancy outcome under prolonged ustekinumab treatment in a patient with Crohn's disease and paradoxical psoriasis. *J Eur Acad Dermatol Venereol* 2016; **30**: e191-e192 [PMID: 26559393 DOI: 10.1111/jdv.13499]

P- Reviewer: Gassler N, Naito Y **S- Editor:** Wang XJ **L- Editor:** A
E- Editor: Huang Y





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: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



ISSN 1007-9327

