ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2017 May 8; 9(13): 613-644

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

Contents

Three issues per month Volume 9 Number 13 May 8, 2017

Contents

World Journal of Hepatology
Volume 9 Number 13 May 8, 2017

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Wei-Bo Yu, MD, PhD, Department of Pathology and Laboratory Medicine, University of California, Los Angeles (UCLA), Los Angeles, CA 90095, United States

AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Hepatology is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, and Scopus.

FLYLEAF

EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
36 Issues/Year (8th, 18th, and 28th of each month)

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Hepatology
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
May 8, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Hepatology

Submit a Manuscript: http://www.f6publishing.com

World J Hepatol 2017 May 8; 9(13): 613-626

DOI: 10.4254/wjh.v9.i13.613

ISSN 1948-5182 (online)

REVIEW

Hepatic complications induced by immunosuppressants and biologics in inflammatory bowel disease

My-Linh Tran-Minh, Paula Sousa, Marianne Maillet, Matthieu Allez, Jean-Marc Gornet

My-Linh Tran-Minh, Paula Sousa, Marianne Maillet, Matthieu Allez, Jean-Marc Gornet, Department of Gastroenterology, AP-HP, Saint Louis Hospital, 75010 Paris, France

Author contributions: Gornet JM designed research and wrote the manuscript; Tran-Minh ML, Sousa P and Maillet M performed literature search and wrote the manuscript; Allez M wrote the manuscript.

Conflict-of-interest statement: Matthieu Allez has received honoraria from MSD, Abbvie, Janssen, Pfizer and GSK. Jean-Marc Gornet has received fees from MSD.

Manuscript source: Invited manuscript

Correspondence to: Dr. Jean-Marc Gornet, Department of Gastroenterology, AP-HP, Saint Louis Hospital, 1 Avenue Claude Vellefaux, 75010 Paris, France. jean-marc.gornet@aphp.fr
Telephone: +33-1-42499575
Fax: +33-1-42499168

Received: March 3, 2017
Peer-review started: March 7, 2017
First decision: March 27, 2017
Revised: April 1, 2017
Accepted: April 23, 2017
Article in press: April 24, 2017
Published online: May 8, 2017

Abstract

The incidence of inflammatory bowel diseases (IBD) is rising worldwide. The therapeutic options for IBD are expanding, and the number of drugs with new targets will rapidly increase in coming years. A rapid step-up approach with close monitoring of intestinal inflammation is extensively used. The fear of side effects represents one the most limiting factor of their use. Despite a widespread use for years, drug induced liver injury (DILI) management remains a challenging situation with Azathioprine and Methotrexate. DILI seems less frequent with anti-tumor necrosis factor agents and new biologic therapies. The aim of this review is to report incidence, physiopathology and practical guidelines in case of DILI occurrence with the armamentarium of old and new drugs in the field of IBD.

Key words: Drug induced liver toxicity; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

Core tip: The therapeutic options for inflammatory bowel disease (IBD) are expanding, and the number of drugs will rapidly increase in coming years. The fear of side effects represents one the most limiting factor of their use. Despite a widespread use for years, drug induced liver injury (DILI) management remains a challenging situation with Azathioprine and Methotrexate. DILI seems less frequent with anti-tumor necrosis factor agents and new biologic therapies. The aim of this review is to report incidence, physiopathology and practical guidelines in case of DILI occurrence with the armamentarium of old and new drugs in the field of IBD.

Tran-Minh ML, Sousa P, Maillet M, Allez M, Gornet JM. Hepatic complications induced by immunosuppressants and biologics in inflammatory bowel disease. *World J Hepatol* 2017; 9(13): 613-626 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i13/613.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i13.613

INTRODUCTION

Inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) mainly involve the intestinal tract. They may be associated with many extra intestinal manifestations[1]. Among them, hepato-biliary manifestations are frequent and often linked with immune disorders (primary sclerosing cholangitis, auto immune hepatitis, overlap syndrome and IgG4 associated cholangiopathy) or drug induced liver injury (DILI)[2]. Approximately 30% of IBD patients will present abnormalities of liver function tests (LFT) during the course of the disease[3]. Over the decades, immunosuppressants (thiopurines, methotrexate, calcineurine inhibitors) and anti-tumor necrosis factor (TNF) agents, took an increasing part in the armamentarium of IBD[4]. More recently, integrin antagonists and interleukine 12/23 inhibitors have emerged in patients refractory or intolerant to anti-TNF therapy[5]. The safety profile of these drugs is an important issue that may limit their use. Acute and/or chronic hepatic injuries directly induced by the treatment or consequently to occurrence or reactivation of an infection have been described with almost all of these treatments. This article reviews the literature regarding hepatic complications of immunosuppressants and biologics in IBD.

Thiopurines

Thiopurines including azathioprine (AZA) and 6-mercaptopurine (6-MP) have been shown to be effective for induction and maintenance of remission in IBD[6,7]. Combination therapy with infliximab plus azathioprine is more likely to induce clinical remission than those receiving azathioprine or infliximab alone in both CD and UC[8,9]. Addition of AZA/6-MP can eliminate antibodies to infliximab in serum and restores clinical response of infliximab in IBD patients[10]. Some studies have also suggested that thioguanine (TG) could be used as an alternative for patient's refractory or intolerant to AZA or 6-MP[11]. AZA and 6-MP have frequent side effects which usually occur within four to six weeks after introduction and concern up to 25% of patients with an annual risk of 7% per patient-year of treatment[12,13]. Depending on its definition, thiopurines hepatotoxicity frequency can vary between 0% and 17%[14,15]. In a large study of 786 patients, LFT elevation was observed in 4% of the population[16]. In a systematic review of 34 studies including a total of 3485 patients, the mean prevalence of AZA/6-MP induced liver disorders was estimated at 3.4% with no difference between both drugs[17]. It has been suggested that the risk of hepatotoxicity was lower in females and higher in CD and active smokers[13,18]. Nonalcoholic fatty liver disease (NAFLD) is increased in IBD patients and has been shown to be an independent risk factor for hepatotoxicity in patients exposed to AZA/6-MP[19]. In a prospective study, use of corticosteroids was associated with an increased risk of AZA/6-MP induced hepatotoxicity whereas anti-TNF had a protective effect[20]. Thus, according to this relatively high frequency, LFT monitoring is mandatory in exposed patients. Adverse reactions to thiopurines can be divided in two groups: Dose independent and dose dependent. The most frequently reported dose-independent events are rash, fever and arthralgia, pancreatitis and hepatitis. It is thought to be immunological mediated and frequently observed in the first weeks of treatment[20]. Dose dependent effects appear later, after months to years, and are correlated with elevated concentration of 6-MMP. Various endothelial cell injuries with resultant raised portal pressures can also developed.

Physiopathology: Purine analogues act as a DNA synthesis inhibitor by incorporation of thiopurine nucleotide metabolite into DNA, leading to both cytotoxicity and immunosuppression[21]. Thiopurines metabolism go through a complex enzymatic pathway. AZA and 6-MP are prodrugs of 6-thioguanine metabolite (6-TGN), the final effective metabolite. AZA is first absorbed and metabolized in the liver to 6-MP which is metabolized by 3 enzymes including thiopurine S-methyltransferase (TPMT) leading to 6-methylmercaptopurine (6-MMP) formation. 6-MMP is a non-effective metabolite but is involved in thiopurine toxicity, particularly hepatotoxicity. Up to 20% of IBD patients preferentially metabolize thiopurines to 6-MMP. Indeed, high 6-MMP level (up to 5700 pmol/8 $\times$ 10^8 erythrocytes) is correlated with a 3-fold increased risk of LFT elevation (18% *vs* 6%)[14]. Various polymorphisms of TPMT gene has been described, leading to different level of enzyme activity: 0.3% of individuals have low or absent TPMT activity, 11% have intermediate activity and 89% have normal activity[22]. TPMT polymorphisms has been mainly associated with hematotoxicity especially neutropenia[23,24]. It was suggested that high TPMT activity could facilitate hepatotoxicity by the accumulation of 6-MMP. However, in a recent meta-analysis of 10 studies including 1875 patients, TPMT polymorphisms were not associated with hepatotoxicity[25]. The mechanisms by which thiopurines cause hepatotoxicity are not well established. A recent study with a proteomic approach suggests that induction of oxidative stress in T-lymphocytes by thiopurines could play an important role[26].

Acute hepatotoxicity: Half of thiopurine DILI occur within the first 3 mo usually prematurely after AZA/6MP introduction[20]. This acute dose independent toxicity is linked to hypersensitivity and idiosyncratic cholestatic reaction non-mediated by IgE reaction. These effects are unrelated to 6-MMP. Clinical symptoms such as fever, rash or lymphadenopathy, hepatomegaly and other biological abnormalities (atypical lymphocytosis, eosinophilia) may be observed concomitantly with elevated LFT. Most of hypersensitive reactions are hepatitis-like picture with moderate elevation of aspartate aminotransferase and alanine aminotransferase (ALT). More rarely, severe cholestatic hepatitis with jaundice

have also been reported with AZA[27,28].

Long term hepatic injury: Nodular regenerative hyperplasia (NRH) is defined by hepatocytes hyperplasia and nodules formation, without fibrosis proliferation separating nodules consecutive to vascular flow variation within liver. It frequently results in portal hypertension (PHT) with its potential complications[29]. NRH may be asymptomatic with normal liver tests for many years[30]. The diagnosis of NRH remains challenging and mainly depends on histological report. However, the interobserver agreement on the histopathologic diagnosis of NRH is flowed, even when assessed by well-experienced liver pathologists[31]. The pathogenesis of NRH in IBD patients is poorly understood but is likely to be multifactorial.

The largest series describing NRH in IBD under thiopurines reported 37 cases in 11 French tertiary centers of the GETAID group. The cumulative risk of NRH was estimated to 0.5% at five years and 1.25% at 10 years. The diagnosis was made after a median time of 48 mo after AZA introduction (range: 6 to 187 mo) and 14 patients (38%) developed PHT during follow-up. Identified risks factors were male sex and stricturing behavior[28]. Another study has shown that the high-risk patient group was males with small bowel resection $\geqslant$ 50 cm either prior to or after AZA initiation[32]. However, IBD in itself can be associated with NRH, and was incidentally found in 6% of thiopurine naive IBD patients undergoing bowel resection[33]. It has been hypothesized that intestinal surgery might promote obliterative portal venopathy by causing malabsorption of vitamins B12, B6 and folic acid, with resultant hyperhomocysteinemia[34]. Some studies have demonstrated that TG treatment (Lanvis©) induced more NRH than AZA or 6-MP[35,36]. In the study by Dubinsky *et al*[35], 33% of the patients treated with TG had NRH at liver biopsy. No association was found with duration of TG treatment, cumulative dose, or TG nucleotide levels. Geller *et al*[37] reported systematic liver biopsies in 37 patients exposed to TG during 1 to 3 years. NHR of varying degree was seen in 20 patients (53%). Another study has suggested that low-dose TG maintenance therapy may be safer[38]. In 28 patients treated at least 30 mo with TG, they observed no histological sign of HNR in 93% of the cases. This finding is reinforced by a recent study which nicely shows in a murine model that sinusoidal obstructive syndrome induced by TG may be avoided by either inhibition of endothelial activation or simple changes to dosing regimens of TG[39]. Nevertheless, regarding the extensive use of newer alternative drugs to thiopurines, TG has been abandoned in clinical practice because of its hepatotoxicity. Natural history of HNR after thiopurines discontinuation remains unclear and either persistent aggravation or improvement have been reported[11,40].

Other vascular disorders associated with thiopurines such as peliosis hepatitis, veno-occlusive disease, hepatoportal sclerosis, sinusoidal dilatation and perisinusoidal fibrosis were also described initially in patients treated for acute leukemia but have been occasionally reported in IBD patients[41-44]. *In vitro* studies with murine sinusoidal endothelial cells and hepatocytes exposed to azathioprine have suggested that the mechanism of hepatotoxicity is sinusoidal endothelial damage associated with glutathione depletion[45].

Management: Most of LFT abnormalities resolve spontaneously or after dose reduction. In a large study with long term follow-up, only 3.6% of patients required treatment cessation for hepatotoxicity[16]. In another study, 90% of patients normalized their liver test after decreasing dose or treatment withdrawal[46]. One of the main questions concerning AZA toxicity management is whether substitution of AZA by 6-MP might affect or decrease hepatotoxicity. In a study of 135 patients with AZA intolerance, 6-MP was well tolerated in almost three quarters of the patients who presented hepatotoxicity (12/17 patients; 71%) suggesting that this option deserves to be tested[47]. Some authors have suggested that routine thiopurines metabolite (especially 6-MMP) monitoring may identify subjects at high risk of hepatotoxicity. Administration of 6-MP twice daily instead of once daily has even been proposed to decreased 6-MMP levels to reduce the risk of hepatotoxicity[46]. Furthermore, twice daily administration decreases 6-MMP levels without affecting 6-TGN levels may lead to equivalent efficacy[48]. Another tool to adapt 6-MMP dosage is coadministration of allopurinol. This drug is a xanthine oxidase inhibitor, an enzyme which metabolizes 6-MP. Xanthine oxidase inhibition leads to increase 6-TGN level by improving drug availability. Since more 6-MP is available for conversion to 6-TGN, a lower dose of thiopurines is sufficient and may avoid toxicity. Safety and effectiveness of long-term allopurinol-thiopurine maintenance treatment in IBD patients has been proven whatever the initial adverse event with increased 6-TGN and decreased 6-MMP concentrations[49,50]. In a pilot study of 11 patients with acute thiopurine hepatotoxicity secondarily treated with allopurinol co-therapy with low-dose AZA or MP, 82% of the patients remained in long-term remission with normal liver tests[51]. A larger study in 25 patients showed similar results with normalization of LFT in 80% of the cases after switch to a combination treatment[52]. It has been shown that 5-ASA daily use results in increased 6-TGN levels and reduced 6-MMP levels with a dose-dependent effect suggesting that salicylates may reduce the risk for hepatotoxic adverse reactions related to AZA/6-MP[53,54]. However, there is a lack of prospective data supporting the therapeutic impact of 5-ASA on AZA/6-MP hepatoxicity prevention. Recently, in a small cohort of 12 patients, no pharmacokinetic interaction was found between adalimumab and thiopurines with comparable concentrations of 6-TGN and 6-MMP before anti-TNF introduction and throughout 12 wk of follow-up[55].

Methotrexate

Methotrexate (MTX) is an antimetabolite with both antiproliferative and immunosuppressive activities impairing DNA synthesis *via* inhibition of dihydrofolate reductase,

decreaded the production of proinflammatory cytokines and lymphocytes apoptosis[56]. Regimens containing MTX are classified as high-dose, intermediate or low dose, determined as dose per unit of body surface area. The management of CD utilized only low dose MTX (< 50 mg/m^2), usually over a long period of time. In this last group the association between MTX and hepatic dysfunction has been extensively studied. In CD, MTX given intramuscularly once weekly at a dose of 25 mg is effective at inducing and maintaining remission in thiopurine-naïve patients[57,58]. Small labelled studies have also suggested efficacy in patients who failed or are intolerant to thiopurines[59,60]. Data are more limited and conflicting in UC[61,62]. In addition, MTX is widely prescribed in combination with biological therapy to reduce immunogenicity and to maintain clinical response[63]. The most common adverse effects involve the gastrointestinal tract such as nausea, vomiting and diarrhea. More serious toxicities such as myelosuppression and abnormal LFT are dose-dependent. Liver toxicity was firstly reported with the use of MTX in psoriasis and inflammatory rheumatic disorders with high initial rate over 25% of the patients. Obesity, alcoholism, diabetes mellitus, previous abnormalities in LFT and a high accumulated dose of MTX were considered as risk factors of liver toxicity in those diseases[64,65]. There is a paucity of studies evaluating liver toxicity as a complication of MTX therapy in the setting of IBD, and no gastroenterology societal recommendations on monitoring for hepatic toxicity have been formulated.

Profile and mechanism of liver injury: Most of understanding of the hepatoxic potential of MTX came from its use in non-malignant disease such has rheumatoid arthritis (RA) and psoriasis.

The mechanism by which MTX adversely affect the liver remains unclear. Liver response to inflammation is fibrosis *via* stellate cell, mediated by metabolite accumulation in liver cell and inhibition of folate metabolite leading to a decreased nucleotid synthesis.

Several polymorphisms in enzymes involved in the metabolism of folic acid are related to the toxicity of MTX. The C677T and A1298C polymorphisms in the MTHFR gene were the most reported, however studies have reported conflicting results. Two meta analyses have been performed. One described an association of the C677T polymorphism with increased toxicity whereas the second found no association between either the C677T or the A1298C polymorphisms of MTHFR and toxicity of MTX in RA[66,67].

Methotrexate can induce a variety of non-specific histologic changes including macrovesiculare steatosis, stellate cell hypertrophy, portal and lobular inflammation and hepatic fibrosis.

Histological toxicity is assessed according to the Roenigk's classification, a subjective and semi quantitative grading liver injury in four 4 groups[68].

Grade findings: (1) Normal; (2) mild fatty infiltration, nuclear variability, or portal inflammation; (3) moderate to severe fatty infiltration, nuclear variability, or portal inflammation and mild fibrosis; (4) moderate to severe fibrosis; and (5) cirrhosis.

DILI frequency: The first case of MTX liver toxicity was described in 1955 in children treated for leukemia. NAFLD syndrome seems to be an independant risk factor associated with DILI under long term low dose methotrexate use[69].

Administration schedule seem to be associated for high, daily dose to liver fibrosis comparing to weekly low dose of MTX. Supplementation with folic acid or folinic acid is associated with reduced incidence of serum transaminase elevation however a relationship between folate depletion and hepatic toxicity has not been fully established[70,71]. The reported incidence of liver enzyme abnormalities in subjects with IBD receiving MTX is variable.

The pooled incidence rate of abnormal hepatic aminotransferase levels (defined as more than 2-fold increase over the upper limit of the normal range) in patients treated with methotrexate for IBD was 1.4 per 100 person-months, while the rate of hepatotoxicity (defined as greater than a 2-fold over the upper limit of the normal range) was 0.9 per 100 person-months. The rate of withdrawal from treatment due to these abnormalities was 0.8 per 100 person-months[72].

It is estimated that 15% to 50% of patients receiving a chronic low dose of MTX therapy will develop elevated LFT, usually mild and limited. In most recent studies, incidence seems lower varying from 5%-10% probably due to co-founding risk factors in initial studies such as alcohol intake, obesity, diabetes mellitus, daily dosing and concomitant use of hepatotoxic drugs increasing[72-74].

In a retrospective study by Fournier on 87 IBD patients with a mean duration of 81 wk and a cumulative dose of 1813 mg, 76% of the population kept normal LFT throughout MTX therapy. Among the patients who developed abnormal LFT, underlying risk factors were found in nearly half of the cases. In 11 patients who have received a cumulative dose exceeding 15000 mg, a liver biopsy found no case of moderate or severe fibrosis (Roenigk ⅢB or Ⅳ) despite abnormal LFT in nine of them. In twenty patients (23%) with abnormal LFT at baseline, spontaneous normalization under MTX was observed in 45% of the cases. Eventually, only 5% of the whole population, needed treatment discontinuation for MTX hepatotoxicity[74].

Another study reporting 20 liver biopsies in patients treated with a cumulative MTX dose of 2633 mg with abnormal LFT in 30% of the cases confirmed the low incidence of severe fibrosis (Roenigk ⅢB in 5%)[75]. These data suggest that abnormal LFT are poorly correlated with liver histology and confirm the low incidence of severe hepatotoxicity and its uncertain relation with cumulated MTX dose.

End stage liver disease is rare under MTX treatment. In a large retrospective study identifying patient who were listed for liver transplantation over 24 years in the United States, only 117 (0.07%) had MTX related

liver disease with characteristic closed to alcoholic liver disease and NAFLD[76].

Management: Patients who undergo MTX therapy should have a careful initial evaluation of historic and physical examination emphasis in alcohol intake, exposure to viral hepatitis, NAFLD risk factors and family history of liver disease.

Regular liver laboratory studies are recommended in patients treated with MTX. Liver biopsy is not recommended routinely during MTX treatment whatever the cumulative dose. However, it should be performed in cases of persistent alteration of transaminases (especially if they do not decrease after reducing the drug dose) and in patients with high accumulated doses, together with other risk factors.

According to RA and psoriasis guidelines[64,65]: Laboratory tests for monitoring hepatotoxicity are recommended, every 2 wk initially for 6 wk to 2 mo and then every 2-3 mo; liver biopsy should be performed in selected cases, in case of sustained liver abnormality (especially in case of persistent abnormal LFT despite dose reduction) or high accumulated doses in patients with others risk factors of hepatotoxicity. Treatment needs to be discontinued in cases of severe fibrosis or cirrhosis; adjusting MTX dose could be proposed in case of liver blood elevation and control in 2 and 4 wk.

Transient elastography (Fibroscan) and non-invasive biochemical methods are emerging as new diagnostic tools to evaluate liver fibrosis in various situations[77]. In a prospective study in CD patients, the median fibroscan values were similar in 33 treated with cumulative dose of more than 1500 mg and 21 patients naïve of Methotrexate[78]. However, this tool could be useful to select patient who should undergo liver biopsy. In a retrospective study of 46 patients treated with MTX for IBD, transient elastography detected six cases of significant fibrosis in patients with normal liver function tests[79]. In a case-control study of 518 patients treated with MTX for various inflammatory diseases, 44 patients (8.5%) had FibroScan and/or FibroTest results suggesting severe liver fibrosis. In a multivariate analysis, the 2 factors associated with abnormal markers of liver fibrosis were high body mass index > 28 kg/m^2 and high alcohol consumption. Neither long MTX duration nor cumulative doses were associated with elevated FibroScan or FibroTest results[78]. These data suggest that transient elastography should be useful mainly in heavy drinkers or patients with NAFLD risk factors treated with MTX.

Anti-TNF

TNF-α is a cytokine produced mainly by macrophages that participates in the regulation of inflammation, cell death and proliferation. This cytokine has proinflammatory and immunoregulatory functions and plays a central role in IBD. TNF-α has also effects in the liver, as a mediator of hepatotoxicity and promotor of hepatocyte proliferation and liver regeneration[80,81]. There are several anti-TNF agents currently approved for the induction and maintenance treatment of IBD, namely infliximab (IFX), adalimumab (ADA), golimumab and certolizumab pegol. Several adverse events have been reported with the use of these agents, such as acute infusion and injection-site reactions, cardiopulmonary and neurologic events, among others[80]. The greatest emphasis has been given to the risk of infections and malignancies, but with an increasing use, other side effects are being uncovered, such as immune-mediated diseases[82,83].

DILI frequency: In the earlier controlled trials of IFX in RA and CD minor elevation of liver enzymes were reported, but extreme elevations were rare, and there were no cases of jaundice or liver failure[84,85]. In a Food and Drug Administration (FDA) post-marketing surveillance program more than 130 cases of liver injury associated with either IFX or etanercept were reported, some of which were fatal or necessitating liver transplantation. This led FDA to issue a safety warning in December 2004 stating that severe hepatic reactions, including acute liver failure, autoimmune hepatitis (AIH) and cholestasis could be caused by IFX[86]. In contrast, ADA hepatotoxic potential appears to be low, usually manifesting as an asymptomatic and transient elevation of liver enzymes[87]. During ADA controlled Phase 3 trials for CD the rate of liver enzymes elevation was similar to the control-treated patients[88]. In a study from Iceland that included patients with IBD, rheumatologic and dermatologic disorders, the absolute risk of DILI associated with IFX was 1 in 120, and with ADA was 1 in 270, but only 11 patients with liver injury were identified in a 5-year period[89]. Even though the numbers were small, no statistically significant differences were found between the rates of DILI of the anti-TNF agents studied. Similar rates had been found in a population-based group from the same group, with a 1 in 148 risk of DILI associated with IFX[90]. However, as data on the propensity of the anti-TNF to cause drug-induced liver disease comes mainly from case reports and small series it is difficult to estimate the absolute and relative risk of hepatic injury associated with these drugs[91,92]. In a retrospective study by Shelton *et al*[93] 1753 IBD patients who initiated anti-TNF therapy (1170 IFX, 575 ADA, 8 certolizumab pegol) were analyzed for new onset ALT elevation. One hundred and two patients (6%) had at least one elevated ALT after initiation of the anti-TNF but in 54 of these patients an alternate cause for liver enzymes elevations was found. Of the 48 patients left (45 due to IFX and 3 to ADA), 4 were considered as highly probable of being caused by anti-TNF. There were no differences in the frequency of concomitant immunomodulator use, either thiopurines or methotrexate. In respect to the newest anti-TNF agents, certolizumab and golimumab, to our knowledge there aren't literature reports of DILI. Nevertheless, FDA label for both of them mentions the risk of hepatitis B virus reactivation and elevation on liver enzymes.

Profile of liver toxicity: In addition to the risk of reactivation of hepatitis B virus (HBV) infection, anti-

TNF are associated with specific patterns of liver injury. The most common presentation is a hepatocellular injury, found in about 75% of the cases[89,92,94,95]. Other presentations are also described, such as a mixed injury pattern with lower peak ALT levels and, more rarely, a cholestatic injury pattern, reported with both IFX and ADA[94,96-98]. Overt liver failure sometimes requiring transplantation has rarely been reported[98-100]. Immunoallergic features such as eosinophilia and rash don't seem to occur frequently in anti-TNF DILI[89,98]. The median latency time to liver enzyme elevation is reported between 13 and 18 wk[89,93,98]. Most patients treated with IFX develop liver injury within the fourth infusion, but, rarely, it can occur after several years of treatment[89,91]. Histologically, a review by Colina *et al*[92] found necroinflammation in the biopsied cases of DILI caused by IFX reported in the literature, but with uneven characteristics between reports. Bridging and massive necrosis were described in the most severe cases. There were also features normally described in AIH such as piecemeal necrosis in the periportal interface and prominent plasma cells. In two cases ductal damage was reported, one of which was diagnosed as overlap syndrome. Rarely, features associated with toxicity such as eosinophils and neutrophils infiltration and ceroid containing Kupffer cells were seen. One of the features of DILI associated with anti-TNF is the presence of autoimmunity markers in some patients, such as positivity for antinuclear (ANA - often with a homogeneous pattern), anti-double-stranded DNA (anti-DsDNA) and anti-smooth muscle antibodies and/or classic histologic features of AIH, already described for IFX[83,91-94,101-104], etanercept and ADA[105-107]. One of the largest series of 34 patients with DILI, have included 26 cases associated with IFX, 6 with ADA and 4 with etanercept[94]. Twenty-two of 33 subjects who underwent serologic analysis (67%) were tested positive for anti-nuclear and/or smooth muscle antibodies and presented both later and higher peak levels of alanine aminotransferase than seronegative patients. Of these 22, 17 underwent liver biopsy and 15 subjects had clear features of autoimmunity. The prognosis was good after drug discontinuation, although some patients had benefit from a course of corticosteroids. It is a challenge to distinguish between AIH and drug-induced-AIH as these entities may have similar clinical, biochemical, serological and histological manifestations, with no pathognomonic features[108]. In a Weiler-Norman and Schramm editorial a specific nomenclature for immune-mediated DILI in 3 categories was proposed[109]. Furthermore, the diseases for which anti-TNF are used may have simultaneous autoimmune disorders and increased autoimmune markers at baseline as part of their immune dysregulation. Lastly, anti-TNF agents can also induce autoantibodies positivity in some patients without the development of liver abnormalities[110-113]. In several of the mentioned studies and case series, a proportion of the patients presenting with autoimmune features were treated with corticosteroids. In some of these patients, there was a decrease or disappearance of autoantibodies with no need of further treatment which suggests an immune-mediated DILI rather than a drug-induced AIH[89,91,92,94]. Of note, there are also cases of malignancies described in patients treated with anti-TNF agents, notably case reports of hepatocellular carcinoma in non-cirrhotic patients[114-116] and of hepatosplenic T cell lymphoma[117-121]. All these patients were in combination treatment with an anti-TNF and a thiopurine, making it difficult to establish the specific role of the anti-TNF agent.

Hepatotoxicity as a class-effect? Even though IFX, etanercept and ADA are all anti-TNF agents that directly bind soluble and membrane-bound TNF-α, they are structurally different. IFX is a chimeric IgG1 monoclonal antibody, ADA a fully humanized IgG1 monoclonal antibody and etanercept (not used in IBD but frequently used in rheumatology) is a soluble TNF-α receptor fusion protein[122]. This might partially explain why patients with a lack of response to one anti-TNF agent benefit from a switch to another anti-TNF. Also, in the past years, polymorphisms in genes encoding proteins related to TNF-α were identified, explaining to some extent the differences in treatment efficacy and toxicity profile[123]. So, even though these drugs were all associated with the development of features of autoimmunity, the capacity in doing so is different for each molecule. In some studies, IFX generated a much higher rate of ANA seroconversion and ANA titer increase than etanercept and ADA[90]. Development of autoantibodies has also been described for certolizumab pegol and golimumab[124,125]. There are already several cases of successful treatment with another anti-TNF after a prior DILI episode[90,93-95,126,127]. This suggests a lack of cross-toxicity within this class of drugs. Etanercept is not a treatment option for IBD, but ADA seems to be a safe alternative in patients who developed liver injury due to IFX and vice-versa.

Mechanism of liver injury: The mechanism by which anti-TNF agents induce DILI is still unknown. Even more puzzling is the fact that some patients develop autoimmune diseases for which anti-TNF are a therapeutic option, such as AIH[109]. As liver injury can occur after only one infusion and is not related to the dose it seems more likely that the hepatotoxicity of anti-TNF agents is idiosyncratic as opposed to dose-dependent[93]. But the complexity of TNF-α role in the liver makes it difficult to draw firm conclusions and several explanations were suggested to date. Genetically predisposed individuals may develop autoimmune diseases triggered by environmental factors. Another possibility is that anti-TNF agents unmask an already existing autoimmune disorder[83]. A third explanation relates to the anti-TNF potential in the generation of autoantibodies. The binding of IFX to the transmembrane TNF-α may lead to apoptosis of monocytes and T-lymphocytes with exposition of nucleosomal autoantigens and formation of autoantibodies[128,129]. The reduced clearance of nuclear debris due to the downregulation of C-reactive protein may also play a role

by prolonged immune system exposure to intracellular material[130]. The structural differences of anti-TNF agents with different binding affinities do membrane TNF-α and different abilities of complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity may explain the different potentials on the induction of autoimmunity[113,128,129,131]. Another hypothesis is that anti-TNF agents inhibit the induction of cytotoxic lymphocytes that would suppress auto reactive B cells, therefore promoting humoral autoimmunity[132]. All these proposed mechanisms try to explain the immune-mediated DILI caused by anti-TNF agents. However, there are several cases without evidence of autoimmunity, in which direct liver damage may be involved[133,134].

Management of DILI associated with anti-TNF: The optimal management of liver injury induced by anti-TNF therapy is still not consensual. The prognosis is generally good, with most patients presenting with mild elevation in liver enzymes resolving spontaneously with continuation of anti-TNF therapy[93]. A consensus statement proposes more restrictive criteria, with avoidance or discontinuation of treatment in patients with transaminases superior to 3 times the upper limit of normal[135]. Many authors have since suggested different management algorithms[91,101,136]. Ideally, before initiation of treatment, a baseline panel of liver enzymes should be obtained, together with a determination of HBV and HCV status[137]. After initiation of treatment, liver enzymes should be monitored periodically, especially during the first three months. When faced with an elevation of liver enzymes, other causes should be excluded, as in any case of suspected DILI. In case of minor elevations of ALT (< 3 times the upper limit of normal), anti-TNF may be continued with close monitoring until resolution. If the enzymes are persistently elevated, superior to 3 times the upper limit of normal or in case of alarm signals such as jaundice, a multidisciplinary approach with refer to an hepatologist and consideration for corticosteroid treatment is advised. A liver biopsy may be useful in this context. If a DILI is documented, anti-TNF withdrawal remains controversial[91,136]. Even though advocated by some authors the interest of routine assessment of autoimmune markers prior to the introduction of an anti-TNF agent is not established[83,91,113,136,138]. Several studies show that this approach doesn't predict the risk of developing subsequent liver injury or autoimmune events and treatment with anti-TNF can be continued in the presence of an asymptomatic ANA seroconversion[89,110,112]. Therefore, routine testing for autoantibodies can't be recommended until further evidence of the clinical implications of these autoantibodies is obtained.

New biologic treatments

Natalizumab and vedolizumab are two integrin antagonists approved for the treatment of IBD. Natalizumab is a humanized recombinant monoclonal antibody that blocks α4β1 and α4β7 integrin-mediated interactions, preventing migration of leukocytes into the gut and brain[139]. Even though its efficacy in the treatment of CD was demonstrated, natalizumab association with a number of cases of progressive multifocal leukoencephalopathy has limited its use[140,141]. Vedolizumab is a humanized monoclonal antibody with specificity to the gut α4β7 integrin with proven efficacy in the treatment of CD and UC[142,143]. Both drugs appeared to have good safety profiles during initial trials. However, on post-marketing surveillance, 6 cases of clinically significant DILI related to natalizumab were reported to FDA, leading to an alteration of its label[144]. In all cases, natalizumab was used for the treatment of multiple sclerosis, and liver injury occurred as early as 6 d after the first administration of the drug. Five of the cases had a hepatocellular pattern of injury, and 3 patients had autoimmune features. One patient had recurrence of the increase of liver enzymes upon readministration of natalizumab, providing evidence that natalizumab was responsible for the injury. There were no deaths nor was a liver transplantation needed. Since then, a case of acute liver failure possibly due to drug-induced AIH and a case of fatal fulminant liver failure due to acute HBV infection in patients treated with natalizumab for multiple sclerosis were reported[145,146]. There were also cases of elevation of transaminases and/or bilirubin in vedolizumab trials for IBD. Ustekinumab is a fully human monoclonal antibody that blocks the activity of interleukin 12/23 shared p40 subunit. This drug has shown efficacy in the treatment of CD, particularly in patients previously treated with IFX[147]. The majority of safety data of ustekinumab comes from dermatologic studies. In PHOENIX 1 and 2[148,149], two studies that evaluated efficacy and safety of ustekinumab in patients with psoriasis, the proportion of patients with liver enzymes abnormalities was low and similar between ustekinumab and control groups. In a small retrospective study including 44 patients with psoriasis treated with ustekinumab, elevation of liver enzymes was mild and uncommon, with no cases of severe DILI[150]. Interleukin-12 is involved in the clearance of HBV by suppressing viral replication, which may explain why patients treated with ustekinumab might be at increased risk of HBV reactivation[151]. Most pivotal studies of ustekinumab excluded patients infected with HBV and HCV; for this reason its safety in this context is not known. In a retrospective study in patients with psoriasis and concurrent HBV infection treated with ustekinumab, 4 patients infected with HBV received antiviral prophylaxis during treatment, without evidence of virus reactivation[152]. Of the 10 patients who didn't receive prophylaxis, 2 fulfilled the criteria for HBV reactivation. In another retrospective study, 3 patients with HCV and 1 patient with HBV under prophylaxis with entecavir were treated with ustekinumab and didn't have an aggravation of the hepatitis[153]. Cases of acute HBV infection/HBV reactivation during ustekinumab treatment and, on the other hand, cases where ustekinumab was safely administered despite HBV or HCV infection were reported recently[154-157]. Even though a real frequency of hepatic adverse events is not yet known for these drugs, this evidence suggests that all patients considered

for biologic treatment should be screened for hepatitis B and C infection prior to introduction of the drug, and liver function should be monitored periodically for the duration of the treatment.

Calcineurine inhibitors

Cyclosporine is a potent immunosupressive drug effective in the treatment of acute severe UC refractory to corticosteroids[158,159]. Tacrolimus is a potential alternative to cyclosporine[160,161]. One of the main limitations to cyclosporine use in clinical practice is its safety profile, namely nephrotoxicity, neurotoxicity and infections, with a need of frequent monitoring[158]. The hepatotoxicity associated with cyclosporine was mainly described in transplant patients. It's generally characterized by a cholestatic pattern due to an impairment of bile formation, probably caused by an interference in the bile secretory apparatus. Liver injury caused by cyclosporine is dose-dependent and can be reduced by a diminution of the dose. Even though the prevalence of liver injury due to cyclosporine was initially estimated to be superior to 50%, this phenomenon was probably due to the use of the drug without blood monitoring, leading to toxic levels of cyclosporine[162]. Studies in IBD patients show a much lower prevalence of hepatotoxicity, between 1% to 4%, generally translated by an elevation in liver enzymes[158,163,164]. In one study, 19% of patients (21/111) developed abnormal liver function tests, but they were only significantly high in one patient[165]. Tacrolimus hepatotoxicity is rare with a similar clinical and biochemical profile to those of cyclosporine. In some cases, there is a lack of cross-reactivity between these two drugs, and one can be used after hepatotoxicity to the other[162]. Nonetheless, hepatotoxicity is generally considered as a rare and minor adverse event with these drugs.

Thalidomide

Thalidomide was initially used to treat morning-sickness associated with pregnancy, until being withdrawn from the market due to its teratogenic effects. Since that, in view of its anti-inflammatory and immunomodulatory properties, it has been reintroduced for the treatment of various diseases including IBD[166,167]. Hepatotoxicity with thalidomide is reported as a rare but serious adverse event. In a review of adverse events reported in the first 18 mo of postmarketing surveillance after thalidomide reintroduction in the market, one case of fatal hepatic failure possibly directly related to thalidomide was identified[168]. In the latest years, other cases with different degrees of severity were reported, mostly in older females treated with thalidomide for multiple myeloma, some of them with an underlying hepatic disease[169-172]. The mechanism of hepatotoxicity of thalidomide remains unclear. The main route of elimination of thalidomide is through non-enzymatic hydrolysis into multiple products in biological fluids and it doesn't seem to undergo significant hepatic metabolism[173].

New investigational treatments

More recently several molecules have shown promising results in IBD and should obtain medical agreement within the next few years. Mongersen, a new oral SMAD 7 antisense oligonucleotide was superior to placebo for inducing clinical remission at day fifteen and maintened for at least two weeks in CD[174]. Increased aminotransferase levels were observed at the dose of 40 mg per day in 5% of the patients but no case was reported at the dose of 10 mg and 160 mg per day.

Tofacitinib, a selective oral inhibitor of the Janus kinase, a family of kinases that mediates signal-transduction activity involving the common gamma chain of the surface receptors for multiple cytokines was superior to placebo for inducing clinical response at week eight in UC[175]. At week twelve, adverse events occurring in $\geqslant$ 5% of patients in any tofacitinib group did not include liver toxicity.

Ozanimod, an oral agonist of the sphingosine-1-phosphate receptor subtypes 1 and 5 that induces peripheral lymphocyte sequestration was superior to placebo at a dose of 1 mg per day for inducing clinical remission at eight weeks[176]. After exposure to up of 32 wk, aspartate aminotransferase increasing was noted in 2% and 1% of patients treated with 0.5 and 1 mg of Ozanimod respectively. These preliminary data suggest that new therapeutic approaches in IBD induce minor hepatoxicity.

REFERENCES

1 **Danese S**, Semeraro S, Papa A, Roberto I, Scaldaferri F, Fedeli G, Gasbarrini G, Gasbarrini A. Extraintestinal manifestations in inflammatory bowel disease. *World J Gastroenterol* 2005; **11**: 7227-7236 [PMID: 16437620 DOI: 10.3748/wjg.v11.i46.7227]

2 **Rojas-Feria M**, Castro M, Suárez E, Ampuero J, Romero-Gómez M. Hepatobiliary manifestations in inflammatory bowel disease: the gut, the drugs and the liver. *World J Gastroenterol* 2013; **19**: 7327-7340 [PMID: 24259964 DOI: 10.3748/wjg.v19.i42.7327]

3 **Mendes FD**, Levy C, Enders FB, Loftus EV, Angulo P, Lindor KD. Abnormal hepatic biochemistries in patients with inflammatory bowel disease. *Am J Gastroenterol* 2007; **102**: 344-350 [PMID: 17100965 DOI: 10.1111/j.1572-0241.2006.00947.x]

4 **Mowat C**, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho GT, Satsangi J, Bloom S. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011; **60**: 571-607 [PMID: 21464096 DOI: 10.1136/gut.2010.224154]

5 **Amiot A**, Peyrin-Biroulet L. Current, new and future biological agents on the horizon for the treatment of inflammatory bowel diseases. *Therap Adv Gastroenterol* 2015; **8**: 66-82 [PMID: 25729432 DOI: 10.1177/1756283X14558193]

6 **Sandborn W**, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. *Cochrane Database Syst Rev* 2000; (**2**): CD000545 [PMID: 10796557 DOI: 10.1002/14651858.CD000545]

7 **Pearson D**, May G, Fick G, Sutherland L. Azathioprine for maintenance of remission in Crohn's disease [Internet]. In: The Cochrane Collaboration. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd, 1998 [cited 2015 Jun 24] [DOI: 10.1002/14651858.CD000067]

8 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175

DOI: 10.1056/NEJMoa0904492]
9 **Panaccione R**, Ghosh S, Middleton S, Márquez JR, Scott BB, Flint L, van Hoogstraten HJ, Chen AC, Zheng H, Danese S, Rutgeerts P. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014; **146**: 392-400.e3 [PMID: 24512909 DOI: 10.1053/j.gastro.2013.10.052]
10 **Ben-Horin S**, Waterman M, Kopylov U, Yavzori M, Picard O, Fudim E, Awadie H, Weiss B, Chowers Y. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**: 444-447 [PMID: 23103905 DOI: 10.1016/j.cgh.2012.10.020]
11 **Herrlinger KR**, Deibert P, Schwab M, Kreisel W, Fischer C, Fellermann K, Stange EF. Remission maintenance by tioguanine in chronic active Crohn's disease. *Aliment Pharmacol Ther* 2003; **17**: 1459-1464 [PMID: 12823147]
12 **Jharap B**, Seinen ML, de Boer NK, van Ginkel JR, Linskens RK, Kneppelhout JC, Mulder CJ, van Bodegraven AA. Thiopurine therapy in inflammatory bowel disease patients: analyses of two 8-year intercept cohorts. *Inflamm Bowel Dis* 2010; **16**: 1541-1549 [PMID: 20155846 DOI: 10.1002/ibd.21221]
13 **Chaparro M**, Ordás I, Cabré E, Garcia-Sanchez V, Bastida G, Peñalva M, Gomollón F, García-Planella E, Merino O, Gutiérrez A, Esteve M, Márquez L, Garcia-Sepulcre M, Hinojosa J, Vera I, Muñoz F, Mendoza JL, Cabriada JL, Montoro MA, Barreiro-de Acosta M, Ceña G, Saro C, Aldeguer X, Barrio J, Maté J, Gisbert JP. Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients. *Inflamm Bowel Dis* 2013; **19**: 1404-1410 [PMID: 23665964 DOI: 10.1097/MIB.0b013e318281f28f]
14 **Dubinsky MC**, Lamothe S, Yang HY, Targan SR, Sinnett D, Théorêt Y, Seidman EG. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology* 2000; **118**: 705-713 [PMID: 10734022]
15 **Hanauer SB**, Korelitz BI, Rutgeerts P, Peppercorn MA, Thisted RA, Cohen RD, Present DH. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004; **127**: 723-729 [PMID: 15362027]
16 **Gisbert JP**, Luna M, González-Lama Y, Pousa ID, Velasco M, Moreno-Otero R, Maté J. Liver injury in inflammatory bowel disease: long-term follow-up study of 786 patients. *Inflamm Bowel Dis* 2007; **13**: 1106-1114 [PMID: 17455203 DOI: 10.1002/ibd.20160]
17 **Gisbert JP**, González-Lama Y, Maté J. Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. *Am J Gastroenterol* 2007; **102**: 1518-1527 [PMID: 17391318 DOI: 10.1111/j.1572-0241.2007.01187.x]
18 **Mazor Y**, Koifman E, Elkin H, Chowers Y, Krivoy N, Karban A, Efrati E. Risk factors for serious adverse effects of thiopurines in patients with Crohn's disease. *Curr Drug Saf* 2013; **8**: 181-185 [PMID: 23845145]
19 **Schröder T**, Schmidt KJ, Olsen V, Möller S, Mackenroth T, Sina C, Lehnert H, Fellermann K, Büning J. Liver steatosis is a risk factor for hepatotoxicity in patients with inflammatory bowel disease under immunosuppressive treatment. *Eur J Gastroenterol Hepatol* 2015; **27**: 698-704 [PMID: 25923946 DOI: 10.1097/MEG.0000000000000350]
20 **Bastida G**, Nos P, Aguas M, Beltrán B, Rubín A, Dasí F, Ponce J. Incidence, risk factors and clinical course of thiopurine-induced liver injury in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2005; **22**: 775-782 [PMID: 16225485 DOI: 10.1111/j.1365-2036.2005.02636.x]
21 **Lennard L**. The clinical pharmacology of 6-mercaptopurine. *Eur J Clin Pharmacol* 1992; **43**: 329-339 [PMID: 1451710]
22 **Weinshilboum RM**, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. *Am J Hum Genet* 1980; **32**: 651-662 [PMID: 7191632]
23 **Colombel JF**, Ferrari N, Debuysere H, Marteau P, Gendre JP, Bonaz B, Soulé JC, Modigliani R, Touze Y, Catala P, Libersa C, Broly F. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. *Gastroenterology* 2000; **118**: 1025-1030 [PMID: 10833476]
24 **Gisbert JP**, Gomollón F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. *Am J Gastroenterol* 2008; **103**: 1783-1800 [PMID: 18557712 DOI: 10.1111/j.1572-0241.2008.01848.x]
25 **Liu YP**, Wu HY, Yang X, Xu HQ, Li YC, Shi DC, Huang JF, Huang Q, Fu WL. Association between thiopurine S-methyltransferase polymorphisms and thiopurine-induced adverse drug reactions in patients with inflammatory bowel disease: a meta-analysis. *PLoS One* 2015; **10**: e0121745 [PMID: 25799415 DOI: 10.1371/journal.pone.0121745]
26 **Misdaq M**, Ziegler S, von Ahsen N, Oellerich M, Asif AR. Thiopurines induce oxidative stress in T-lymphocytes: a proteomic approach. *Mediators Inflamm* 2015; **2015**: 434825 [PMID: 25873760 DOI: 10.1155/2015/434825]
27 **Roda G**, Caponi A, Belluzzi A, Roda E. Severe cholestatic acute hepatitis following azathioprine therapy in a patient with ulcerative pancolitis. *Dig Liver Dis* 2009; **41**: 914-915 [PMID: 19376754 DOI: 10.1016/j.dld.2009.03.004]
28 **Romagnuolo J**, Sadowski DC, Lalor E, Jewell L, Thomson AB. Cholestatic hepatocellular injury with azathioprine: a case report and review of the mechanisms of hepatotoxicity. *Can J Gastroenterol* 1998; **12**: 479-483 [PMID: 9812167]
29 **Ghabril M**, Vuppalanchi R. Drug-induced nodular regenerative hyperplasia. *Semin Liver Dis* 2014; **34**: 240-245 [PMID: 24879987 DOI: 10.1055/s-0034-1375963]
30 **Reshamwala PA**, Kleiner DE, Heller T. Nodular regenerative hyperplasia: not all nodules are created equal. *Hepatology* 2006; **44**: 7-14 [PMID: 16799965 DOI: 10.1002/hep.21258]
31 **Jharap B**, van Asseldonk DP, de Boer NK, Bedossa P, Diebold J, Jonker AM, Leteurtre E, Verheij J, Wendum D, Wrba F, Zondervan PE, Colombel JF, Reinisch W, Mulder CJ, Bloemena E, van Bodegraven AA. Diagnosing Nodular Regenerative Hyperplasia of the Liver Is Thwarted by Low Interobserver Agreement. *PLoS One* 2015; **10**: e0120299 [PMID: 26054009 DOI: 10.1371/journal.pone.0120299]
32 **Seksik P**, Mary JY, Beaugerie L, Lémann M, Colombel JF, Vernier-Massouille G, Cosnes J. Incidence of nodular regenerative hyperplasia in inflammatory bowel disease patients treated with azathioprine. *Inflamm Bowel Dis* 2011; **17**: 565-572 [PMID: 20848502 DOI: 10.1002/ibd.21330]
33 **De Boer NK**, Tuynman H, Bloemena E, Westerga J, Van Der Peet DL, Mulder CJ, Cuesta MA, Meuwissen SG, Van Nieuwkerk CM, Van Bodegraven AA. Histopathology of liver biopsies from a thiopurine-naïve inflammatory bowel disease cohort: prevalence of nodular regenerative hyperplasia. *Scand J Gastroenterol* 2008; **43**: 604-608 [PMID: 18415755 DOI: 10.1080/00365520701800266]
34 **Musumba CO**. Review article: the association between nodular regenerative hyperplasia, inflammatory bowel disease and thiopurine therapy. *Aliment Pharmacol Ther* 2013; **38**: 1025-1037 [PMID: 24099468 DOI: 10.1111/apt.12490]
35 **Dubinsky MC**, Vasiliauskas EA, Singh H, Abreu MT, Papadakis KA, Tran T, Martin P, Vierling JM, Geller SA, Targan SR, Poordad FF. 6-thioguanine can cause serious liver injury in inflammatory bowel disease patients. *Gastroenterology* 2003; **125**: 298-303 [PMID: 12891528 DOI: 10.1016/S0016-5085(03)00938-7]
36 **De Bruyne R**, Portmann B, Samyn M, Bansal S, Knisely A, Mieli-Vergani G, Dhawan A. Chronic liver disease related to 6-thioguanine in children with acute lymphoblastic leukaemia. *J Hepatol* 2006; **44**: 407-410 [PMID: 16226335 DOI: 10.1016/j.jhep.2005.06.020]
37 **Geller SA**, Dubinsky MC, Poordad FF, Vasiliauskas EA, Cohen AH, Abreu MT, Tran T, Martin P, Vierling JM, Targan SR. Early hepatic nodular hyperplasia and submicroscopic fibrosis associated with 6-thioguanine therapy in inflammatory bowel disease. *Am J*

Surg Pathol 2004; **28**: 1204-1211 [PMID: 15316320]
38 **de Boer NK**, Zondervan PE, Gilissen LP, den Hartog G, Westerveld BD, Derijks LJ, Bloemena E, Engels LG, van Bodegraven AA, Mulder CJ. Absence of nodular regenerative hyperplasia after low-dose 6-thioguanine maintenance therapy in inflammatory bowel disease patients. *Dig Liver Dis* 2008; **40**: 108-113 [PMID: 18083079 DOI: 10.1016/j.dld.2007.10.013]
39 **Oancea I**, Png CW, Das I, Lourie R, Winkler IG, Eri R, Subramaniam N, Jinnah HA, McWhinney BC, Levesque JP, McGuckin MA, Duley JA, Florin TH. A novel mouse model of veno-occlusive disease provides strategies to prevent thioguanine-induced hepatic toxicity. *Gut* 2013; **62**: 594-605 [PMID: 22773547 DOI: 10.1136/gutjnl-2012-302274]
40 **Teml A**, Schwab M, Harrer M, Miehsler W, Schaeffeler E, Dejaco C, Mantl M, Schneider B, Vogelsang H, Reinisch W. A prospective, open-label trial of 6-thioguanine in patients with ulcerative or indeterminate colitis. *Scand J Gastroenterol* 2005; **40**: 1205-1213 [PMID: 16265777]
41 **Larrey D**, Fréneaux E, Berson A, Babany G, Degott C, Valla D, Pessayre D, Benhamou JP. Peliosis hepatis induced by 6-thioguanine administration. *Gut* 1988; **29**: 1265-1269 [PMID: 3198003]
42 **Tuyama AC**, Krakauer M, Alzaabi M, Fiel MI, Legnani P, Schiano TD. Mercaptopurine-induced hepatoportal sclerosis in a patient with Crohn's disease. *J Crohns Colitis* 2013; **7**: 590-593 [PMID: 22841133 DOI: 10.1016/j.crohns.2012.07.006]
43 **Holtmann M**, Schreiner O, Köhler H, Denzer U, Neurath M, Galle PR, Höhler T. Veno-occlusive disease (VOD) in Crohn's disease (CD) treated with azathioprine. *Dig Dis Sci* 2003; **48**: 1503-1505 [PMID: 12924643]
44 **Russmann S**, Zimmermann A, Krähenbühl S, Kern B, Reichen J. Veno-occlusive disease, nodular regenerative hyperplasia and hepatocellular carcinoma after azathioprine treatment in a patient with ulcerative colitis. *Eur J Gastroenterol Hepatol* 2001; **13**: 287-290 [PMID: 11293451]
45 **DeLeve LD**, Wang X, Kuhlenkamp JF, Kaplowitz N. Toxicity of azathioprine and monocrotaline in murine sinusoidal endothelial cells and hepatocytes: the role of glutathione and relevance to hepatic venoocclusive disease. *Hepatology* 1996; **23**: 589-599 [PMID: 8617441 DOI: 10.1002/hep.510230326]
46 **Shaye OA**, Yadegari M, Abreu MT, Poordad F, Simon K, Martin P, Papadakis KA, Ippoliti A, Vasiliauskas E, Tran TT. Hepatotoxicity of 6-mercaptopurine (6-MP) and Azathioprine (AZA) in adult IBD patients. *Am J Gastroenterol* 2007; **102**: 2488-2494 [PMID: 17764490 DOI: 10.1111/j.1572-0241.2007.01515.x]
47 **Hindorf U**, Johansson M, Eriksson A, Kvifors E, Almer SH. Mercaptopurine treatment should be considered in azathioprine intolerant patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2009; **29**: 654-661 [PMID: 19183142 DOI: 10.1111/j.1365-2036.2008.03925.x]
48 **Shih DQ**, Nguyen M, Zheng L, Ibanez P, Mei L, Kwan LY, Bradford K, Ting C, Targan SR, Vasiliauskas EA. Split-dose administration of thiopurine drugs: a novel and effective strategy for managing preferential 6-MMP metabolism. *Aliment Pharmacol Ther* 2012; **36**: 449-458 [PMID: 22784257 DOI: 10.1111/j.1365-2036.2012.05206.x]
49 **Hoentjen F**, Seinen ML, Hanauer SB, de Boer NK, Rubin DT, Bouma G, Harrell LE, van Bodegraven AA. Safety and effectiveness of long-term allopurinol-thiopurine maintenance treatment in inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 363-369 [PMID: 22605661 DOI: 10.1002/ibd.23021]
50 **Ansari A**, Patel N, Sanderson J, O'Donohue J, Duley JA, Florin TH. Low-dose azathioprine or mercaptopurine in combination with allopurinol can bypass many adverse drug reactions in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2010; **31**: 640-647 [PMID: 20015102 DOI: 10.1111/j.1365-2036.2009.04221.x]
51 **Ansari A**, Elliott T, Baburajan B, Mayhead P, O'Donohue J, Chocair P, Sanderson J, Duley J. Long-term outcome of using allopurinol co-therapy as a strategy for overcoming thiopurine hepatotoxicity in treating inflammatory bowel disease. *Aliment Pharmacol Ther* 2008; **28**: 734-741 [PMID: 19145729]
52 **Smith MA**, Blaker P, Marinaki AM, Anderson SH, Irving PM, Sanderson JD. Optimising outcome on thiopurines in inflammatory bowel disease by co-prescription of allopurinol. *J Crohns Colitis* 2012; **6**: 905-912 [PMID: 22386736 DOI: 10.1016/j.crohns.2012.02.007]
53 **de Graaf P**, de Boer NK, Wong DR, Karner S, Jharap B, Hooymans PM, Veldkamp AI, Mulder CJ, van Bodegraven AA, Schwab M. Influence of 5-aminosalicylic acid on 6-thioguanosine phosphate metabolite levels: a prospective study in patients under steady thiopurine therapy. *Br J Pharmacol* 2010; **160**: 1083-1091 [PMID: 20590602 DOI: 10.1111/j.1476-5381.2010.00731.x]
54 **de Boer NK**, Wong DR, Jharap B, de Graaf P, Hooymans PM, Mulder CJ, Rijmen F, Engels LG, van Bodegraven AA. Dose-dependent influence of 5-aminosalicylates on thiopurine metabolism. *Am J Gastroenterol* 2007; **102**: 2747-2753 [PMID: 17764493 DOI: 10.1111/j.1572-0241.2007.01511.x]
55 **Wong DR**, Pierik M, Seinen ML, van Bodegraven AA, Gilissen LP, Bus P, Bakker JA, Masclee AA, Neef C, Engels LG, Hooymans PM. The pharmacokinetic effect of adalimumab on thiopurine metabolism in Crohn's disease patients. *J Crohns Colitis* 2014; **8**: 120-128 [PMID: 23932783 DOI: 10.1016/j.crohns.2013.07.004]
56 **Chan ES**, Cronstein BN. Methotrexate--how does it really work? *Nat Rev Rheumatol* 2010; **6**: 175-178 [PMID: 20197777 DOI: 10.1038/nrrheum.2010.5]
57 **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]
58 **Feagan BG**, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, Greenberg GR, Koval J, Wong CJ, Hopkins M, Hanauer SB, McDonald JW. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000; **342**: 1627-1632 [PMID: 10833208 DOI: 10.1056/NEJM200006013422202]
59 **Lémann M**, Zenjari T, Bouhnik Y, Cosnes J, Mesnard B, Rambaud JC, Modigliani R, Cortot A, Colombel JF. Methotrexate in Crohn's disease: long-term efficacy and toxicity. *Am J Gastroenterol* 2000; **95**: 1730-1734 [PMID: 10925976 DOI: 10.1111/j.1572-0241.2000.02190.x]
60 **Wahed M**, Louis-Auguste JR, Baxter LM, Limdi JK, McCartney SA, Lindsay JO, Bloom SL. Efficacy of methotrexate in Crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine /mercaptopurine. *Aliment Pharmacol Ther* 2009; **30**: 614-620 [PMID: 19552632 DOI: 10.1111/j.1365-2036.2009.04073.x]
61 **Mañosa M**, García V, Castro L, García-Bosch O, Chaparro M, Barreiro-de Acosta M, Carpio D, Aguas M. Methotrexate in ulcerative colitis: a Spanish multicentric study on clinical use and efficacy. *J Crohns Colitis* 2011; **5**: 397-401 [PMID: 21939912 DOI: 10.1016/j.crohns.2011.03.012]
62 **Seinen ML**, Ponsioen CY, de Boer NK, Oldenburg B, Bouma G, Mulder CJ, van Bodegraven AA. Sustained clinical benefit and tolerability of methotrexate monotherapy after thiopurine therapy in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2013; **11**: 667-672 [PMID: 23333660 DOI: 10.1016/j.cgh.2012.12.026]
63 **Feagan BG**, McDonald JW, Panaccione R, Enns RA, Bernstein CN, Ponich TP, Bourdages R, Macintosh DG, Dallaire C, Cohen A, Fedorak RN, Paré P, Bitton A, Saibil F, Anderson F, Donner A, Wong CJ, Zou G, Vandervoort MK, Hopkins M, Greenberg GR. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. *Gastroenterology* 2014; **146**: 681-688.e1 [PMID: 24269926 DOI: 10.1053/j.gastro.2013.11.024]
64 **Kalb RE**, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol* 2009; **60**: 824-837 [PMID: 19389524 DOI: 10.1016/j.jaad.2008.11.906]
65 **Visser K**, Katchamart W, Loza E, Martinez-Lopez JA, Salliot

C, Trudeau J, Bombardier C, Carmona L, van der Heijde D, Bijlsma JW, Boumpas DT, Canhao H, Edwards CJ, Hamuryudan V, Kvien TK, Leeb BF, Martín-Mola EM, Mielants H, Müller-Ladner U, Murphy G, Østergaard M, Pereira IA, Ramos-Remus C, Valentini G, Zochling J, Dougados M. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; **68**: 1086-1093 [PMID: 19033291 DOI: 10.1136/ard.2008.094474]

66 **Fisher MC**, Cronstein BN. Metaanalysis of methylenetetrahydrofolate reductase (MTHFR) polymorphisms affecting methotrexate toxicity. *J Rheumatol* 2009; **36**: 539-545 [PMID: 19208607 DOI: 10.3899/jrheum.080576]

67 **Cáliz R**, del Amo J, Balsa A, Blanco F, Silva L, Sanmarti R, Martínez FG, Collado MD, Ramirez Mdel C, Tejedor D, Artieda M, Pascual-Salcedo D, Oreiro N, Andreu JL, Graell E, Simon L, Martínez A, Mulero J. The C677T polymorphism in the MTHFR gene is associated with the toxicity of methotrexate in a Spanish rheumatoid arthritis population. *Scand J Rheumatol* 2012; **41**: 10-14 [PMID: 22044028 DOI: 10.3109/03009742.2011.617312]

68 **Berends MA**, van Oijen MG, Snoek J, van de Kerkhof PC, Drenth JP, Han van Krieken J, de Jong EM. Reliability of the Roenigk classification of liver damage after methotrexate treatment for psoriasis: a clinicopathologic study of 160 liver biopsy specimens. *Arch Dermatol* 2007; **143**: 1515-1519 [PMID: 18087000 DOI: 10.1001/archderm.143.12.1515]

69 **Langman G**, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. *J Gastroenterol Hepatol* 2001; **16**: 1395-1401 [PMID: 11851839]

70 **Shea B**, Swinden MV, Tanjong Ghogomu E, Ortiz Z, Katchamart W, Rader T, Bombardier C, Wells GA, Tugwell P. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev* 2013; (**5**): CD000951 [PMID: 23728635 DOI: 10.1002/14651858.CD000951.pub2]

71 **Prey S**, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. *Br J Dermatol* 2009; **160**: 622-628 [PMID: 18945303 DOI: 10.1111/j.1365-2133.2008.08876.x]

72 **Khan N**, Abbas AM, Whang N, Balart LA, Bazzano LA, Kelly TN. Incidence of liver toxicity in inflammatory bowel disease patients treated with methotrexate: a meta-analysis of clinical trials. *Inflamm Bowel Dis* 2012; **18**: 359-367 [PMID: 21751301 DOI: 10.1002/ibd.21820]

73 **Suares NC**, Hamlin PJ, Greer DP, Warren L, Clark T, Ford AC. Efficacy and tolerability of methotrexate therapy for refractory Crohn's disease: a large single-centre experience. *Aliment Pharmacol Ther* 2012; **35**: 284-291 [PMID: 22112005 DOI: 10.1111/j.1365-2036.2011.04925.x]

74 **Fournier MR**, Klein J, Minuk GY, Bernstein CN. Changes in liver biochemistry during methotrexate use for inflammatory bowel disease. *Am J Gastroenterol* 2010; **105**: 1620-1626 [PMID: 20160715 DOI: 10.1038/ajg.2010.21]

75 **Te HS**, Schiano TD, Kuan SF, Hanauer SB, Conjeevaram HS, Baker AL. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. *Am J Gastroenterol* 2000; **95**: 3150-3156 [PMID: 11095334 DOI: 10.1111/j.1572-0241.2000.03287.x]

76 **Dawwas MF**, Aithal GP. End-stage methotrexate-related liver disease is rare and associated with features of the metabolic syndrome. *Aliment Pharmacol Ther* 2014; **40**: 938-948 [PMID: 25185870 DOI: 10.1111/apt.12912]

77 **Barbero-Villares A**, Mendoza Jiménez-Ridruejo J, Taxonera C, López-Sanromán A, Pajares R, Bermejo F, Pérez-Calle JL, Mendoza JL, Algaba A, Moreno-Otero R, Maté J, Gisbert JP. Evaluation of liver fibrosis by transient elastography (Fibroscan®) in patients with inflammatory bowel disease treated with methotrexate: a multicentric trial. *Scand J Gastroenterol* 2012; **47**: 575-579 [PMID: 22229701 DOI: 10.3109/00365521.2011.647412]

78 **Laharie D**, Seneschal J, Schaeverbeke T, Doutre MS, Longy-Boursier M, Pellegrin JL, Chabrun E, Villars S, Zerbib F, de Lédinghen V. Assessment of liver fibrosis with transient elastography and FibroTest in patients treated with methotrexate for chronic inflammatory diseases: a case-control study. *J Hepatol* 2010; **53**: 1035-1040 [PMID: 20801541 DOI: 10.1016/j.jhep.2010.04.043]

79 **González-Lama Y**, Taxonera C, López-Sanromán A, Pérez-Calle JL, Bermejo F, Pajares R, McNicholl AG, Opio V, Mendoza JL, López P, Algaba A, Estelles J, Barbero A, Mendoza J, Maté J, Gisbert JP. Methotrexate in inflammatory bowel disease: a multicenter retrospective study focused on long-term efficacy and safety. The Madrid experience. *Eur J Gastroenterol Hepatol* 2012; **24**: 1086-1091 [PMID: 22713509 DOI: 10.1097/MEG.0b013e3283556db5]

80 **Nielsen OH**, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. *N Engl J Med* 2013; **369**: 754-762 [PMID: 23964937 DOI: 10.1056/NEJMct1209614]

81 **Wullaert A**, van Loo G, Heyninck K, Beyaert R. Hepatic tumor necrosis factor signaling and nuclear factor-kappaB: effects on liver homeostasis and beyond. *Endocr Rev* 2007; **28**: 365-386 [PMID: 17431229 DOI: 10.1210/er.2006-0031]

82 **Sousa P**, Allez M. Complications of biologics in inflammatory bowel disease. *Curr Opin Gastroenterol* 2015; **31**: 296-302 [PMID: 26039721 DOI: 10.1097/MOG.0000000000000191]

83 **Ramos-Casals M**, Brito-Zerón P, Soto MJ, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies. *Best Pract Res Clin Rheumatol* 2008; **22**: 847-861 [PMID: 19028367 DOI: 10.1016/j.berh.2008.09.008]

84 **Maini R**, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999; **354**: 1932-1939 [PMID: 10622295]

85 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. 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]

86 **Drugs@FDA**. FDA Approved Drug Products [Internet]. [cited 2015 Feb 4]. Available from: URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

87 **Mease PJ**, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, Birbara C, Thomson GT, Perdok RJ, Medich J, Wong RL, Gladman DD. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). *Ann Rheum Dis* 2009; **68**: 702-709 [PMID: 18684743 DOI: 10.1136/ard.2008.092767]

88 **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]

89 **Björnsson ES**, Gunnarsson BI, Gröndal G, Jonasson JG, Einarsdottir R, Ludviksson BR, Gudbjörnsson B, Olafsson S. Risk of drug-induced liver injury from tumor necrosis factor antagonists. *Clin Gastroenterol Hepatol* 2015; **13**: 602-608 [PMID: 25131534 DOI: 10.1016/j.cgh.2014.07.062]

90 **Björnsson ES**, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; **144**: 1419-1425, 1425.e1-3; quiz e19-20 [PMID: 23419359 DOI: 10.1053/j.gastro.2013.02.006]

91 **Mancini S**, Amorotti E, Vecchio S, Ponz de Leon M, Roncucci L. Infliximab-related hepatitis: discussion of a case and review of the literature. *Intern Emerg Med* 2010; **5**: 193-200 [PMID: 20107930 DOI: 10.1007/s11739-009-0342-4]

92 **Colina F**, Molero A, Casís B, Martínez-Montiel P. Infliximab-

related hepatitis: a case study and literature review. *Dig Dis Sci* 2013; **58**: 3362-3367 [PMID: 23645381 DOI: 10.1007/s10620-013-2698-6]
93 **Shelton E**, Chaudrey K, Sauk J, Khalili H, Masia R, Nguyen DD, Yajnik V, Ananthakrishnan AN. New onset idiosyncratic liver enzyme elevations with biological therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; **41**: 972-979 [PMID: 25756190 DOI: 10.1111/apt.13159]
94 **Ghabril M**, Bonkovsky HL, Kum C, Davern T, Hayashi PH, Kleiner DE, Serrano J, Rochon J, Fontana RJ, Bonacini M. Liver injury from tumor necrosis factor-α antagonists: analysis of thirty-four cases. *Clin Gastroenterol Hepatol* 2013; **11**: 558-564.e3 [PMID: 23333219 DOI: 10.1016/j.cgh.2012.12.025]
95 **Parekh R**, Kaur N. Liver Injury Secondary to Anti-TNF-Alpha Therapy in Inflammatory Bowel Disease: A Case Series and Review of the Literature. *Case Rep Gastrointest Med* 2014; **2014**: 956463 [PMID: 24707412 DOI: 10.1155/2014/956463]
96 **Menghini VV**, Arora AS. Infliximab-associated reversible cholestatic liver disease. *Mayo Clin Proc* 2001; **76**: 84-86 [PMID: 11155419 DOI: 10.4065/76.1.84]
97 **Kim E**, Bressler B, Schaeffer DF, Yoshida EM. Severe cholestasis due to adalimumab in a Crohn's disease patient. *World J Hepatol* 2013; **5**: 592-595 [PMID: 24179620 DOI: 10.4254/wjh.v5.i10.592]
98 **Tobon GJ**, Cañas C, Jaller JJ, Restrepo JC, Anaya JM. Serious liver disease induced by infliximab. *Clin Rheumatol* 2007; **26**: 578-581 [PMID: 16547695 DOI: 10.1007/s10067-005-0169-y]
99 **Kinnunen U**, Färkkilä M, Mäkisalo H. A case report: ulcerative colitis, treatment with an antibody against tumor necrosis factor (infliximab), and subsequent liver necrosis. *J Crohns Colitis* 2012; **6**: 724-727 [PMID: 22398069 DOI: 10.1016/j.crohns.2012.02.004]
100 **Hagel S**, Bruns T, Theis B, Herrmann A, Stallmach A. Subacute liver failure induced by adalimumab. *Int J Clin Pharmacol Ther* 2011; **49**: 38-40 [PMID: 21176723]
101 **Dang LJ**, Lubel JS, Gunatheesan S, Hosking P, Su J. Drug-induced lupus and autoimmune hepatitis secondary to infliximab for psoriasis. *Australas J Dermatol* 2014; **55**: 75-79 [PMID: 23651182 DOI: 10.1111/ajd.12054]
102 **Marques M**, Magro F, Cardoso H, Carneiro F, Portugal R, Lopes J, Costa Santos C. Infliximab-induced lupus-like syndrome associated with autoimmune hepatitis. *Inflamm Bowel Dis* 2008; **14**: 723-725 [PMID: 17929297 DOI: 10.1002/ibd.20293]
103 **Doyle A**, Forbes G, Kontorinis N. Autoimmune hepatitis during infliximab therapy for Crohn's disease: a case report. *J Crohns Colitis* 2011; **5**: 253-255 [PMID: 21575891 DOI: 10.1016/j.crohns.2010.12.007]
104 **Saleem G**, Li SC, MacPherson BR, Cooper SM. Hepatitis with interface inflammation and IgG, IgM, and IgA anti-double-stranded DNA antibodies following infliximab therapy: comment on the article by Charles et al. *Arthritis Rheum* 2001; **44**: 1966-1968 [PMID: 11508453 DOI: 10.1002/1529-0131(200108)44:8<1966::AID-ART339>3.0.CO;2-3]
105 **Nakayama S**. Autoimmune Hepatitis Triggered by Anti-TNF-α Therapy. *Case Rep Med* 2013; **2013**: 561748 [PMID: 24082887 DOI: 10.1155/2013/561748]
106 **Titos Arcos JC**, Hallal H, Robles M, Andrade RJ. Recurrent hepatotoxicity associated with etanercept and adalimumab but not with infliximab in a patient with rheumatoid arthritis. *Rev Esp Enferm Dig* 2012; **104**: 282-284 [PMID: 22662786]
107 **Adar T**, Mizrahi M, Pappo O, Scheiman-Elazary A, Shibolet O. Adalimumab-induced autoimmune hepatitis. *J Clin Gastroenterol* 2010; **44**: e20-e22 [PMID: 19593165 DOI: 10.1097/MCG.0b013e3181a745e7]
108 **Efe C**. Drug induced autoimmune hepatitis and TNF-α blocking agents: is there a real relationship? *Autoimmun Rev* 2013; **12**: 337-339 [PMID: 22841985 DOI: 10.1016/j.autrev.2012.03.010]
109 **Weiler-Normann C**, Schramm C. Drug induced liver injury and its relationship to autoimmune hepatitis. *J Hepatol* 2011; **55**: 747-749 [PMID: 21396413 DOI: 10.1016/j.jhep.2011.02.024]
110 **Takase K**, Horton SC, Ganesha A, Das S, McHugh A, Emery P, Savic S, Buch MH. What is the utility of routine ANA testing in predicting development of biological DMARD-induced lupus and vasculitis in patients with rheumatoid arthritis? Data from a single-centre cohort. *Ann Rheum Dis* 2014; **73**: 1695-1699 [PMID: 24854356 DOI: 10.1136/annrheumdis-2014-205318]
111 **Atzeni F**, Ardizzone S, Sarzi-Puttini P, Colombo E, Maconi G, De Portu S, Carrabba M, Bianchi Porro G. Autoantibody profile during short-term infliximab treatment for Crohn's disease: a prospective cohort study. *Aliment Pharmacol Ther* 2005; **22**: 453-461 [PMID: 16128684 DOI: 10.1111/j.1365-2036.2005.02576.x]
112 **Vermeire S**, Noman M, Van Assche G, Baert F, Van Steen K, Esters N, Joossens S, Bossuyt X, Rutgeerts P. Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study. *Gastroenterology* 2003; **125**: 32-39 [PMID: 12851868]
113 **Caramaschi P**, Bambara LM, Pieropan S, Tinazzi I, Volpe A, Biasi D. Anti-TNFalpha blockers, autoantibodies and autoimmune diseases. *Joint Bone Spine* 2009; **76**: 333-342 [PMID: 19539516 DOI: 10.1016/j.jbspin.2008.12.008]
114 **Murakami A**, Tanaka Y, Ueda M, Nagano Y, Kunisaki R, Morimoto M, Enaka M, Tanabe M, Kawachi K, Sasaki T, Nozawa A. Hepatocellular carcinoma occurring in a young Crohn's disease patient. *Pathol Int* 2009; **59**: 492-496 [PMID: 19563414 DOI: 10.1111/j.1440-1827.2009.02399.x]
115 **Chen SC**, Cummings OW, Hartley MP, Filomena CA, Cho WK. Hepatocellular carcinoma occurring in a patient with Crohn's disease treated with both azathioprine and infliximab. *Dig Dis Sci* 2006; **51**: 952-955 [PMID: 16670938 DOI: 10.1007/s10620-005-9009-9]
116 **Fortinsky KJ**, Alali A, Jeejeebhoy K, Fischer S, Sherman M, Fung S. Metastatic hepatocellular carcinoma in a patient with Crohn's disease treated with azathioprine and infliximab: a case report and literature review. *Case Rep Gastrointest Med* 2014; **2014**: 340836 [PMID: 25587469 DOI: 10.1155/2014/340836]
117 **Kotlyar DS**, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M, Sampat S, Mendizabal M, Lin MV, Lichtenstein GR. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011; **9**: 36-41.e1 [PMID: 20888436 DOI: 10.1016/j.cgh.2010.09.016]
118 **Thai A**, Prindiville T. Hepatosplenic T-cell lymphoma and inflammatory bowel disease. *J Crohns Colitis* 2010; **4**: 511-522 [PMID: 21122554 DOI: 10.1016/j.crohns.2010.05.006]
119 **Mackey AC**, Green L, Leptak C, Avigan M. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease: update. *J Pediatr Gastroenterol Nutr* 2009; **48**: 386-388 [PMID: 19274799]
120 **Thayu M**, Markowitz JE, Mamula P, Russo PA, Muinos WI, Baldassano RN. Hepatosplenic T-cell lymphoma in an adolescent patient after immunomodulator and biologic therapy for Crohn disease. *J Pediatr Gastroenterol Nutr* 2005; **40**: 220-222 [PMID: 15699701]
121 **Ochenrider MG**, Patterson DJ, Aboulafia DM. Hepatosplenic T-cell lymphoma in a young man with Crohn's disease: case report and literature review. *Clin Lymphoma Myeloma Leuk* 2010; **10**: 144-148 [PMID: 20371449 DOI: 10.3816/CLML.2010.n.021]
122 **Mpofu S**, Fatima F, Moots RJ. Anti-TNF-alpha therapies: they are all the same (aren't they?). *Rheumatology* (Oxford) 2005; **44**: 271-273 [PMID: 15561736 DOI: 10.1093/rheumatology/keh483]
123 **Kooloos WM**, de Jong DJ, Huizinga TW, Guchelaar HJ. Potential role of pharmacogenetics in anti-TNF treatment of rheumatoid arthritis and Crohn's disease. *Drug Discov Today* 2007; **12**: 125-131 [PMID: 17275732 DOI: 10.1016/j.drudis.2006.11.013]
124 **Schreiber S**, Khaliq-Kareemi M, Lawrance IC, Thomsen OØ, Hanauer SB, McColm J, Bloomfield R, Sandborn WJ. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007; **357**: 239-250 [PMID: 17634459 DOI: 10.1056/NEJMoa062897]
125 **Zidi I**, Bouaziz A, Ben Amor N. Golimumab and immunogenicity? 2010 and beyond. *Pharmazie* 2011; **66**: 233-243 [PMID: 21612149]
126 **Féau S**, Causse X, Corondan A, Michenet P, Autret-Leca E.

[Acute drug-induced hepatitis during adalimumab and ibuprofen treatment]. *Gastroenterol Clin Biol* 2010; **34**: 420-422 [PMID: 20494537 DOI: 10.1016/j.gcb.2010.01.017]

127 **Thiéfin G**, Morelet A, Heurgué A, Diebold MD, Eschard JP. Infliximab-induced hepatitis: absence of cross-toxicity with etanercept. *Joint Bone Spine* 2008; **75**: 737-739 [PMID: 18693125 DOI: 10.1016/j.jbspin.2007.12.009]

128 **Van den Brande JM**, Braat H, van den Brink GR, Versteeg HH, Bauer CA, Hoedemaeker I, van Montfrans C, Hommes DW, Peppelenbosch MP, van Deventer SJ. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology* 2003; **124**: 1774-1785 [PMID: 12806611]

129 **Cantaert T**, De Rycke L, Mavragani CP, Wijbrandts CA, Niewold TB, Niers T, Vandooren B, Veys EM, Richel D, Tak PP, Crow MK, Baeten D. Exposure to nuclear antigens contributes to the induction of humoral autoimmunity during tumour necrosis factor alpha blockade. *Ann Rheum Dis* 2009; **68**: 1022-1029 [PMID: 18625621 DOI: 10.1136/ard.2008.093724]

130 **Gershov D**, Kim S, Brot N, Elkon KB. C-Reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: implications for systemic autoimmunity. *J Exp Med* 2000; **192**: 1353-1364 [PMID: 11067883]

131 **Mitoma H**, Horiuchi T, Tsukamoto H, Tamimoto Y, Kimoto Y, Uchino A, To K, Harashima S, Hatta N, Harada M. Mechanisms for cytotoxic effects of anti-tumor necrosis factor agents on transmembrane tumor necrosis factor alpha-expressing cells: comparison among infliximab, etanercept, and adalimumab. *Arthritis Rheum* 2008; **58**: 1248-1257 [PMID: 18438840 DOI: 10.1002/art.23447]

132 **Via CS**, Shustov A, Rus V, Lang T, Nguyen P, Finkelman FD. In vivo neutralization of TNF-alpha promotes humoral autoimmunity by preventing the induction of CTL. *J Immunol* 2001; **167**: 6821-6826 [PMID: 11739498]

133 **Carlsen KM**, Riis L, Madsen OR. Toxic hepatitis induced by infliximab in a patient with rheumatoid arthritis with no relapse after switching to etanercept. *Clin Rheumatol* 2009; **28**: 1001-1003 [PMID: 19370307 DOI: 10.1007/s10067-009-1179-y]

134 **Kluger N**, Girard C, Guillot B, Bessis D. Efficiency and safety of etanercept after acute hepatitis induced by infliximab for psoriasis. *Acta Derm Venereol* 2009; **89**: 332-334 [PMID: 19479148 DOI: 10.2340/00015555-0619]

135 **Miehsler W**, Novacek G, Wenzl H, Vogelsang H, Knoflach P, Kaser A, Dejaco C, Petritsch W, Kapitan M, Maier H, Graninger W, Tilg H, Reinisch W. A decade of infliximab: The Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. *J Crohns Colitis* 2010; **4**: 221-256 [PMID: 21122513 DOI: 10.1016/j.crohns.2009.12.001]

136 **Rossi RE**, Parisi I, Despott EJ, Burroughs AK, O'Beirne J, Conte D, Hamilton MI, Murray CD. Anti-tumour necrosis factor agent and liver injury: literature review, recommendations for management. *World J Gastroenterol* 2014; **20**: 17352-17359 [PMID: 25516646 DOI: 10.3748/wjg.v20.i46.17352]

137 **Rahier JF**, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, Cottone M, de Ridder L, Doherty G, Ehehalt R, Esteve M, Katsanos K, Lees CW, Macmahon E, Moreels T, Reinisch W, Tilg H, Tremblay L, Veereman-Wauters G, Viget N, Yazdanpanah Y, Eliakim R, Colombel JF. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014; **8**: 443-468 [PMID: 24613021 DOI: 10.1016/j.crohns.2013.12.013]

138 **Bonacini M**, Ghabril M, Bonkovsky HL. Hepatotoxicity of anti-TNF agents. *Dig Dis Sci* 2014; **59**: 1070-1071 [PMID: 24652111 DOI: 10.1007/s10620-014-3109-3]

139 **Sandborn WJ**, Yednock TA. Novel approaches to treating inflammatory bowel disease: targeting alpha-4 integrin. *Am J Gastroenterol* 2003; **98**: 2372-2382 [PMID: 14638336 DOI: 10.1111/j.1572-0241.2003.08703.x]

140 **Sandborn WJ**, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione R, Sanders M, Schreiber S, Targan S, van Deventer S, Goldblum R, Despain D, Hogge GS, Rutgeerts P. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2005; **353**: 1912-1925 [PMID: 16267322 DOI: 10.1056/NEJMoa043335]

141 **Bloomgren G**, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, Lee S, Plavina T, Scanlon JV, Sandrock A, Bozic C. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012; **366**: 1870-1880 [PMID: 22591293 DOI: 10.1056/NEJMoa1107829]

142 **Feagan BG**, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013; **369**: 699-710 [PMID: 23964932 DOI: 10.1056/NEJMoa1215734]

143 **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. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369**: 711-721 [PMID: 23964933 DOI: 10.1056/NEJMoa1215739]

144 **Bezabeh S**, Flowers CM, Kortepeter C, Avigan M. Clinically significant liver injury in patients treated with natalizumab. *Aliment Pharmacol Ther* 2010; **31**: 1028-1035 [PMID: 20163378 DOI: 10.1111/j.1365-2036.2010.04262.x]

145 **Lisotti A**, Azzaroli F, Brillanti S, Mazzella G. Severe acute autoimmune hepatitis after natalizumab treatment. *Dig Liver Dis* 2012; **44**: 356-357 [PMID: 22154948 DOI: 10.1016/j.dld.2011.11.003]

146 **Hillen ME**, Cook SD, Samanta A, Grant E, Quinless JR, Rajasingham JK. Fatal acute liver failure with hepatitis B virus infection during nataluzimab treatment in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm* 2015; **2**: e72 [PMID: 25815364 DOI: 10.1212/NXI.0000000000000072]

147 **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. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012; **367**: 1519-1528 [PMID: 23075178 DOI: 10.1056/NEJMoa1203572]

148 **Leonardi CL**, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB. 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]

149 **Papp KA**, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu MC, Wang Y, Li S, Dooley LT, Reich K. 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]

150 **Llamas-Velasco M**, Concha-Garzón MJ, García-Diez A, Daudén E. Liver Injury in Psoriasis Patients Receiving Ustekinumab: A Retrospective Study of 44 Patients Treated in the Clinical Practice Setting. *Actas Dermosifiliogr* 2015; **106**: 470-476 [PMID: 25912374 DOI: 10.1016/j.ad.2015.02.002]

151 **Rossol S**, Marinos G, Carucci P, Singer MV, Williams R, Naoumov NV. Interleukin-12 induction of Th1 cytokines is important for viral clearance in chronic hepatitis B. *J Clin Invest* 1997; **99**: 3025-3033 [PMID: 9185527 DOI: 10.1172/JCI119498]

152 **Chiu HY**, Chen CH, Wu MS, Cheng YP, Tsai TF. The safety profile of ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B or C. *Br J Dermatol* 2013; **169**: 1295-1303 [PMID: 23746170 DOI: 10.1111/bjd.12461]

153 **Navarro R**, Vilarrasa E, Herranz P, Puig L, Bordas X, Carrascosa JM, Taberner R, Ferrán M, García-Bustinduy M, Romero-Maté A, Pedragosa R, García-Diez A, Daudén E. Safety and effectiveness

of ustekinumab and antitumour necrosis factor therapy in patients with psoriasis and chronic viral hepatitis B or C: a retrospective, multicentre study in a clinical setting. *Br J Dermatol* 2013; **168**: 609-616 [PMID: 22985451 DOI: 10.1111/bjd.12045]
154 **Abuchar A**, Vitiello M, Kerdel FA. Psoriasis treated with ustekinumab in a patient with hepatitis C. *Int J Dermatol* 2013; **52**: 381-382 [PMID: 23414168 DOI: 10.1111/j.1365-4632.2011.04876.x]
155 **Koskinas J**, Tampaki M, Doumba PP, Rallis E. Hepatitis B virus reactivation during therapy with ustekinumab for psoriasis in a hepatitis B surface-antigen-negative anti-HBs-positive patient. *Br J Dermatol* 2013; **168**: 679-680 [PMID: 23121260 DOI: 10.1111/bjd.12120]
156 **Steglich RB**, Meneghello LP, Carvalho AV, Cheinquer H, Muller FM, Reginatto FP. The use of ustekinumab in a patient with severe psoriasis and positive HBV serology. *An Bras Dermatol* 2014; **89**: 652-654 [PMID: 25054756]
157 **Opel D**, Economidi A, Chan D, Wasfi Y, Mistry S, Vergou T, Antoniou C, Sofen H. Two cases of hepatitis B in patients with moderate to severe psoriasis with ustekinumab. *J Drugs Dermatol* 2012; **11**: 1498-1501 [PMID: 23377523]
158 **García-López S**, Gomollón-García F, Pérez-Gisbert J. Cyclosporine in the treatment of severe attack of ulcerative colitis: a systematic review. *Gastroenterol Hepatol* 2005; **28**: 607-614 [PMID: 16373009]
159 **Lichtiger S**, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; **330**: 1841-1845 [PMID: 8196726 DOI: 10.1056/NEJM199406303302601]
160 **Benson A**, Barrett T, Sparberg M, Buchman AL. Efficacy and safety of tacrolimus in refractory ulcerative colitis and Crohn's disease: a single-center experience. *Inflamm Bowel Dis* 2008; **14**: 7-12 [PMID: 17879277 DOI: 10.1002/ibd.20263]
161 **Ogata H**, Matsui T, Nakamura M, Iida M, Takazoe M, Suzuki Y, Hibi T. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006; **55**: 1255-1262 [PMID: 16484504 DOI: 10.1136/gut.2005.081794]
162 **Reuben A**. Chapter 31 - Hepatotoxicity of Immunosuppressive Drugs A2 - Kaplowitz, Neil [Internet]. In: DeLeve LD. Drug-Induced Liver Disease (Third Edition). Boston: Academic Press, 2013 [cited 2016 May 6]: 569-591. Available from: URL: http://www.sciencedirect.com/science/article/pii/B9780123878175000315
163 **Arts J**, D'Haens G, Zeegers M, Van Assche G, Hiele M, D'Hoore A, Penninckx F, Vermeire S, Rutgeerts P. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. *Inflamm Bowel Dis* 2004; **10**: 73-78 [PMID: 15168804]
164 **Rogler G**. Gastrointestinal and liver adverse effects of drugs used for treating IBD. *Best Pract Res Clin Gastroenterol* 2010; **24**: 157-165 [PMID: 20227029 DOI: 10.1016/j.bpg.2009.10.011]
165 **Sternthal MB**, Murphy SJ, George J, Kornbluth A, Lichtiger S, Present DH. Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 937-943 [PMID: 18177449 DOI: 10.1111/j.1572-0241.2007.01718.x]
166 **Yang C**, Singh P, Singh H, Le ML, El-Matary W. Systematic review: thalidomide and thalidomide analogues for treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; **41**: 1079-1093 [PMID: 25858208 DOI: 10.1111/apt.13181]
167 **Tseng S**, Pak G, Washenik K, Pomeranz MK, Shupack JL. Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. *J Am Acad Dermatol* 1996; **35**: 969-979 [PMID: 8959957]
168 **Clark TE**, Edom N, Larson J, Lindsey LJ. Thalomid (Thalidomide) capsules: a review of the first 18 months of spontaneous post-marketing adverse event surveillance, including off-label prescribing. *Drug Saf* 2001; **24**: 87-117 [PMID: 11235821]
169 **Vilas-Boas F**, Gonçalves R, Sobrinho Simões M, Lopes J, Macedo G. Thalidomide-induced acute cholestatic hepatitis: case report and review of the literature. *Gastroenterol Hepatol* 2012; **35**: 560-566 [PMID: 22789729 DOI: 10.1016/j.gastrohep.2012.05.007]
170 **Hanje AJ**, Shamp JL, Thomas FB, Meis GM. Thalidomide-induced severe hepatotoxicity. *Pharmacotherapy* 2006; **26**: 1018-1022 [PMID: 16803426 DOI: 10.1592/phco.26.7.1018]
171 **Dabak V**, Kuriakose P. Thalidomide-induced severe hepatotoxicity. *Cancer Chemother Pharmacol* 2009; **63**: 583-585 [PMID: 19083237 DOI: 10.1007/s00280-008-0891-7]
172 **Hamadani M**, Benson DM, Copelan EA. Thalidomide-induced fulminant hepatic failure. *Mayo Clin Proc* 2007; **82**: 638 [PMID: 17493431 DOI: 10.4065/82.5.638]
173 **Franks ME**, Macpherson GR, Figg WD. Thalidomide. *Lancet* 2004; **363**: 1802-1811 [PMID: 15172781 DOI: 10.1016/S0140-6736(04)16308-3]
174 **Monteleone G**, Neurath MF, Ardizzone S, Di Sabatino A, Fantini MC, Castiglione F, Scribano ML, Armuzzi A, Caprioli F, Sturniolo GC, Rogai F, Vecchi M, Atreya R, Bossa F, Onali S, Fichera M, Corazza GR, Biancone L, Savarino V, Pica R, Orlando A, Pallone F. Mongersen, an oral SMAD7 antisense oligonucleotide, and Crohn's disease. *N Engl J Med* 2015; **372**: 1104-1113 [PMID: 25785968 DOI: 10.1056/NEJMoa1407250]
175 **Sandborn WJ**, Ghosh S, Panes J, Vranic I, Su C, Rousell S, Niezychowski W. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012; **367**: 616-624 [PMID: 22894574 DOI: 10.1056/NEJMoa1112168]
176 **Sandborn WJ**, Feagan BG. Ozanimod Treatment for Ulcerative Colitis. *N Engl J Med* 2016; **375**: e17 [PMID: 27557326 DOI: 10.1056/NEJMc1607287]

P- Reviewer: Kojecky V, Lee SD, Sonzogni A **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, 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