Systematic review/Meta-analysis

Drug-induced liver injury secondary to biologic medications in inflammatory bowel disease: meta-analysis and systematic review

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Abstract

Introduction: Drug-induced hepatotoxicity and biologic drugs have historically been challenging in inflammatory bowel disease (IBD). We aimed to study the prevalence of hepatotoxicity in adult patients using biologic medications.

Material and methods: With the guidelines described by PRISMA-P, a detailed search strategy for each electronic database was developed based on the one used for PubMed, Medline, and Embase. We included prospective and retrospective randomized controlled trials (RCTs) that assessed the efficacy and hepatotoxicity of biologics in IBD patients. Hepatotoxicity was defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2× upper limit of normal or cholestasis. We used Review Manager 5 (RevMan5) to analyse the data. We calculated the odds ratio (OR) with a 95% confidence interval (CI). We assessed heterogeneity using the χ^2 test and the I^2 statistic.

Results: We identified 862 records in total. After we had removed duplicates 564 records were left for review. Four studies did not report on how participants were randomized to treatment groups or how allocation concealment was achieved; we rated these studies at unclear risk of bias for these domains. There was no presence of any heterogeneity among studies (χ^2 = 2.21, df = 6, p = 0.90, and I^2 = 0%), when all seven studies were involved for analysis. Our meta-analysis was conducted on the fixed effects model, with 0.770, 95% CI (–0.630, 0.957), and p = 0.02. Hepatotoxicity was not related to any tumor necrosis factor α antagonist. Thiopurine-induced liver injury occurred more frequently within the first months of treatment, 50% of cases within the first 3 months. However, risk of hepatotoxicity above the third quartile (6-MMPR > 5,300) was 5 times that below the third quartile (11.4% vs. 2.3%, p < 0.05).

Conclusions: This study summed up the broad information on occurrence of biologic-related hepatotoxicity in IBD patients in a clinical practice setting. When hepatotoxicity occurred, the treatment was withdrawn in 31% of patients, but an important percentage, 44%, were able to continue the full dose of thiopurine once the dose was temporarily adjusted. This group of patients had a dose-dependent hepatotoxicity rather than an immunologic hepatitis.

Key words: drug-induced liver injury, inflammatory bowel diseases, hepatotoxicity.

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD), collectively known as inflammatory bowel disease (IBD), are both characterized by diffuse inflammation of the bowel [1]. CD is a chronic, episodic, inflammatory condition of the gastrointestinal system, with affected regions consisting of transmural ulceration separated by normal mucosa [2]. The small intestine is most commonly affected, although the large intestine may also be involved. Common symptoms include abdominal pain, diarrhoea, weight loss, bleeding, nausea and vomiting [3]. Abdominal complications may include bowel obstruction, perforation, abscesses, fistulas, and peri-anal disease [4]. About 20% of people with CD experience extra-intestinal complications that may include musculoskeletal, ocular, dermatologic, hepato-biliary, renal and haematological conditions [5]. On the other hand, UC is an idiopathic inflammatory condition of the colon which results in diffuse friability and superficial erosions on the colonic wall associated with bleeding [6]. It is the most common form of IBD worldwide [7]. It typically consists of inflammation limited to the mucosa and sub mucosa of the colon [8]. Typically, the disease starts in the rectum and extends proximally in a continuous manner [9]. The cause of IBD is not known, but it seems to occur in genetically disposed people in response to environmental factors [10]. UC is almost certainly an autoimmune disease initiated by an inflammatory response to colonic bacteria [11]. Conservative medications for irritable bowel disease such as UC and CD include anti-inflammatory drugs, immune suppressants and corticosteroids [12]. If an individual does not respond, or loses response to first-line treatments, then biologic therapies such as tumour necrosis factor-α (TNF-α) antagonists, e.g. adalimumab, are considered for treating irritable bowel disease [13]. Maintenance of remission of IBD is a clinically important goal, as disease relapse can negatively affect quality of life [14]. Amongst the most commonly prescribed treatments for several chronic inflammatory diseases one of the categories of medications is biologics [15]. TNF-α inhibitors, more so than other agents, have been observed to cause drug-induced liver injury. Additionally, because the approval and popularity of checkpoint inhibitors have grown, similar patterns of liver injury have been documented, with a majority of cases describing immune-mediated hepatitis [16]. Although the exact mechanism of injury is unknown, various host and medication characteristics play a role in the outcome of the molecular cascade invoked by biologics [17]. Prognosis is usually favourable with cessation of the damage causing agent, but cases of acute liver failure requiring liver transplantation have also been observed [18]. Therefore, algorithms have been created to assist clinicians in treating drug-induced autoimmune hepatitis, mostly with corticosteroids [19]. Additionally, case reports have documented successfully re-challenging patients with a different biologic without recurrence of liver injury, but data are limited [20]. Further investigation is warranted regarding the potential for cross-reactivity and mechanism of injury to develop guidelines to aid clinicians in further management of these patients [21].

Hepatobiliary disorders are common in patients with IBD, and persistent abnormal liver function tests are found in approximately 20% to 30% of individuals with IBD. In most cases, the cause of these elevations will fall into 1 of 3 main categories [22]. They can be as a result of extraintestinal manifestations of the disease process, related to medication toxicity, or the result of an underlying primary hepatic disorder unrelated to IBD [23]. Biologic therapy to inhibit TNF-α, a pro-inflammatory cytokine, has become a widely used, safe, and effective treatment for patients with IBD [24]. For more than the past two decades, biologic therapies have revolutionized the care for people with IBD, but each therapy has its own risks, together with the likelihood of liver damage. Numerous classes of biologics for the treatment of IBD now exist [25]. TNF-α inhibitors were the first biologic class approved for use, in 1998. The mechanism of action of these monoclonal antibodies (mAbs) is directed against proinflammatory TNF molecules, which are frequently increased in IBD patients [26]. It has also been reported that he development of anti-drug antibodies with biologic therapy possibly will have positive implications for long-term management [27]. Hence, it was essential to carry out a review study of the hepatotoxicity caused by biologics given for treatment of UC and CD, in IBD patients.

Material and methods

Search methods for identification of studies

Detailed search strategies for each electronic database were developed based on the one used for PubMed (Ovid) Medline, and (Ovid) Embase but with appropriate database related search strategy modification such as the use of truncations, wildcards, and filters [28]. The subject search used a combination of the controlled vocabulary terms "Mesh terms" and free-text words based on the search strategy developed for Medline.

We searched the following databases with English language restriction applied in each database until 2020 from the studies' inception.

- Medline (Ovid)
- Embase (Ovid)

- PubMed
- Cochrane IBD Group Specialized Register.

We followed the guidelines described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [29].

This review covered controlled trials in which a biologic was administered to one study group; the control group may or may not have received a placebo.

Criteria for considering studies for this review

Types of studies

We included prospective and retrospective RCTs that assessed the efficacy and hepatotoxicity of biologics in IBD patients.

Types of participants

This review includes participants of any age who have been diagnosed with UC and CD, using clinical, radiological, endoscopic or histological criteria.

Types of interventions

This review includes trials that compared any biologic either to a placebo or to an active comparator.

Outcome measures

Studies done on efficacy and adverse effects, such as liver injury by biologics in IBD patients.

Data collection and analysis

Two authors independently assessed the titles and abstracts of studies identified by the search criteria to determine eligibility according to the inclusion criteria. We discussed disagreements until we reached a consensus among the review authors, and consulted with a third review author when we could not reach agreement. The characteristics of all included studies are presented in Table I.

Data extraction and management

Two review authors independently extracted data using a standardized extraction form. Eventually the extracted information was as follows:

1. General information (type of publication, title, journal, year);
2. Study design features (method of randomization, concealment of allocation and blinding, power calculation, dates of enrolment and follow-up, study);
3. Eligibility (number of participants screened and their randomization);
4. Participant characteristics (age, sex, race, severity of disease, current and prior medications);
5. Intervention (dose and type of medication, and whether it was compared to placebo or active comparator);
6. Primary and secondary outcomes;
7. Follow-up (dates of follow-up along with withdrawals and number of participants lost to follow-up);
8. Funding details and author conflicts of interest.

Assessment of risk of bias in included studies

Two review authors independently assessed risks of bias using the Cochrane 'Risk of bias' tool [30]. We assessed several study characteristics for risks of bias, including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and

Table I. The characteristics of all included studies

Study ID	Methods	Participants	Interventions	Outcomes
Bastida *et al.* 2005	Prospective randomized study	Aged 18–75 with CD	6-mercaptopurine, azathioprine	Liver toxicity, drugs' adverse effects
Koller *et al.* 2017	Prospective randomized study	Aged 39; 30.0–52.75 with IBD	Infliximab, azathioprine	Mucosal healing, drugs' adverse effects
Paul *et al.* 2013	Prospective randomized study	Aged 34.6–64.8 with IBD	Infliximab	Drug adverse effects
Schnitzler *et al.* 2009	Prospective randomized study	Aged 35.8 (25.7–44.6) with IBD	Infliximab	Drug adverse effects
Tapete *et al.* 2018	Prospective randomized study	Aged 35–64 with CD	Adalimumab (ADL) or infliximab	GI healing, drug adverse effects
Tighe *et al.* 2017	Prospective randomized study	Aged (38–44) with IBD	Adalimumab (ADL) or infliximab	Drug adverse effects
Warman *et al.* 2015	Prospective randomized study	Aged (30–53) with IBD	Infliximab, 6-mercaptopurine azathioprine	Drug adverse effects

other potential sources of bias. Based on these criteria, the studies were rated as having a low, high or unclear risk of bias for each category. We discussed any disagreements about risks of bias and then brought them to a third review author as necessary.

Statistical analysis

Review Manager 5 (RevMan5) was used to analyse the data. For dichotomous outcomes, the odds ratio (OR) was calculated with a 95% confidence interval (CI).

Assessment of heterogeneity

The heterogeneity was assessed using the χ^2 test and the I^2 statistic [31]. We considered an I^2 value of less than 25% indicative of low heterogeneity, greater than 50% indicative of moderate heterogeneity and greater than 75% high heterogeneity.

For the χ^2 test, a p-value of 0.10 was considered to be statistically significant. If the I^2 statistic and χ^2 test suggested heterogeneity, we visually inspected the forest plot for outliers. Thus a sensitivity analysis (e.g. excluding outliers) to explore potential explanations for heterogeneity was used.

Assessment of reporting biases

Funnel plots were used to assess publication bias found between the studies, which are presented in Figure 1 [32].

Data synthesis

We combined data from individual trials for meta-analysis when interventions, participant groups and outcomes were sufficiently similar. A consensus was developed between the team to discuss the disagreement. The pooled OR was calculated with a 95% CI for dichotomous outcomes. As there was no significant heterogeneity within our study we used a fixed-effects model to pool the data.

Sensitivity analysis

We used sensitivity analysis to examine the impact of the following variables on the pooled effect estimate:

1. Random-effects versus fixed-effect modelling;
2. Low risk of bias versus unclear or high risk of bias;
3. Relevant loss to follow-up (more than 10%);
4. Full-text articles versus abstract or unpublished studies.

Results

Description of studies – results of the search

Our literature search identified 862 records in total. After we had removed duplicates 564 records were left for review. Two review authors independently reviewed the titles and abstracts of these records and selected 40 full-text articles for review. We further excluded thirty-one studies with different reasons and finally seven studies [33–39] (total of 896 participants) met the predefined inclusion criteria and were included in this review (Figure 2).

Risk of bias in included studies

The methodological quality of each study was assessed using the Cochrane 'Risk of bias' tool and we summarize our findings in Figure 3.

Allocation

Four studies did not report on how participants were randomized to treatment groups or how allocation concealment was achieved; hence, these studies were rated at unclear risk of bias for these domains [35, 36, 38, 39].

Blinding

Two studies did not report on how blinding was maintained for participants, personnel or outcome assessors throughout the study time period; hence these studies have been rated at unclear risk of bias for these domains [38, 40].

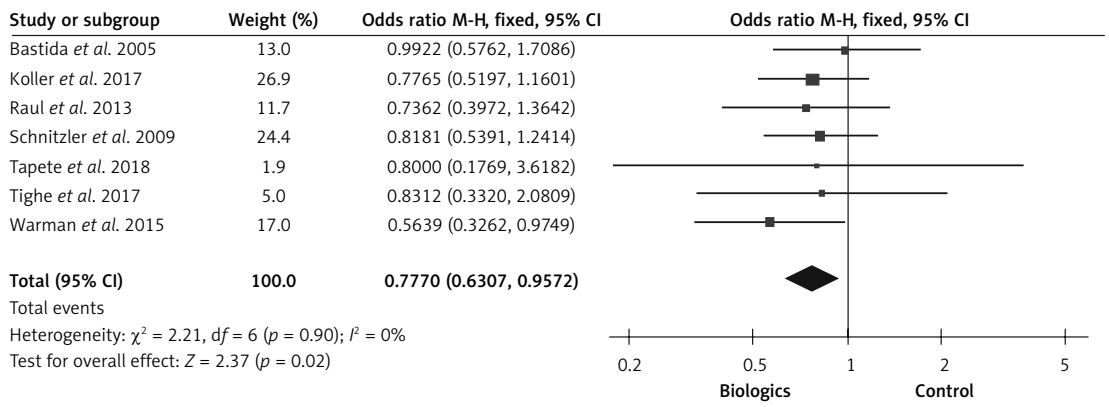

Figure 1. Forest plot of all included studies

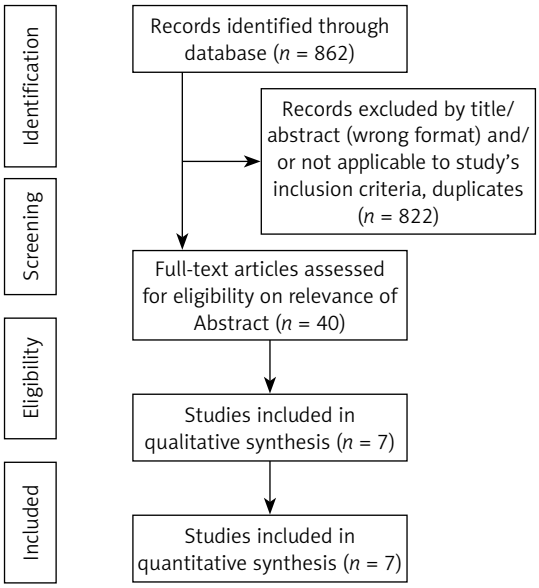

Figure 2. PRISMA flow diagram

Incomplete outcome data

One study [39] did not report on the number of participants who were initially randomized, so we could not determine the number of participants who had withdrawn during the study period; thus, the study has been rated at unclear risk of bias for this domain.

Selective reporting

All of the included studies reported on all expected outcomes and were rated at low risk of bias for this domain.

Other potential sources of bias

Five of the included studies appeared to have other potential sources of bias and were rated at low risk of bias for this domain [35, 36, 38–40].

Results of pooled data

All of our included trials mentioned adverse effect of biologics on liver which are analysed statistically and the results are summarized in Figure 3.

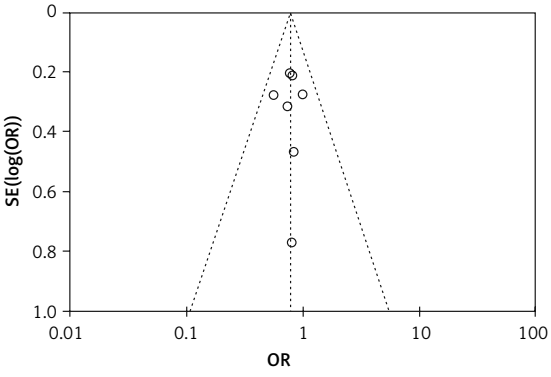

Figure 4. Funnel plot

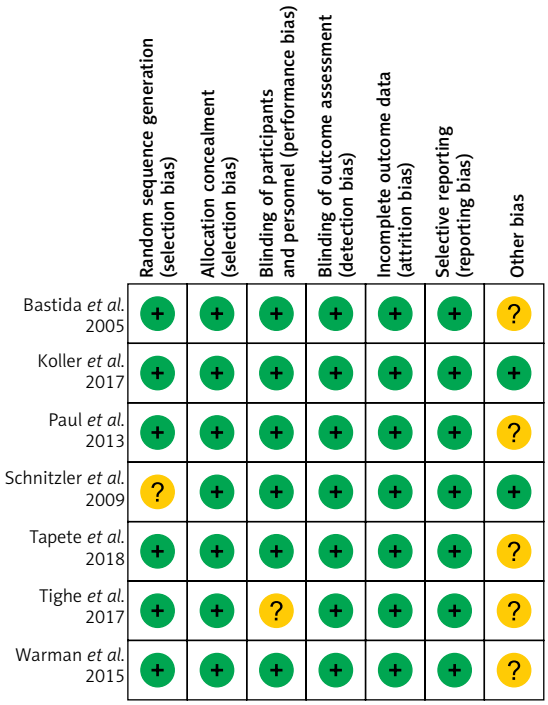

Figure 3. Risk of bias summary

There was no presence of any heterogeneity among studies (χ^2 = 2.21, df = 6, p = 0.90, and I^2= 0%), when the whole seven studies were involved for analysis. Our meta-analysis was conducted on the fixed effects model, with the (0.770, 95% CI (–0.630, 0.957), and p = 0.02.

Publication bias

The funnel plot was generated based on the mean adverse events; a funnel plot was applied to evaluate the publication biases of all seven studies. Summarized in Figure 4, the outcome suggests that there was not significant publication bias.

Discussion

This review includes seven studies which are prospective observational studies that examined the efficacy and safety of biologics in IBD patients. Warman *et al.* 2015 stated that therapeutic drug monitoring of infliximab is not common care in the daily practice of a gastroenterologist treating IBD. Lack of effectiveness or the manifestation of side effects may often be encountered by dose or interval adjustments before turning to therapeutic drug monitoring. Therefore, these trough levels are not based on a standard regime, as we see in patients newly started on infliximab, but might be influenced by the adjustments [41]. Their study provided insights into infliximab trough levels in our IBD cohort in which dose adjustments had already been performed and whether there is still an association with remission [39]. In 2005 Bastida *et al.* mentioned for the first time about occurrence

of hepatotoxicity in IBD patients treated with thiopurinic immunomodulators [42]. The occurrence of abnormal liver function tests (LFTs) or liver toxicity is a relevant finding during the follow-up of patients treated with thiopurinic immunomodulators, as was shown in their study conducted with a cohort of 161 IBD patients [43]. There is a lack of recent published series that specifically assess thiopurine-induced hepatotoxicity, but some recent studies with IBD patients do not describe any case of liver injury during the follow-up [33]. Probably the main limitation of studies evaluating drug-induced liver toxicity is related to diagnosis, due to the absence of specific markers or tests. Therefore, the diagnosis relied entirely on circumstantial evidence and only in the cases of relapse after rechallenge did we have the certainty that azathioprine or mercaptopurine was the offending drug [44]. Liver biopsy is an invasive procedure with significant morbidity and was not performed routinely in all patients presenting with abnormal LFTs. However, liver biopsy is not required to establish the diagnosis of drug-induced liver toxicity. Based on the absence of histological confirmation and on the fact that an important percentage of patients were able to tolerate full-dose therapy, we cannot assert that we are dealing with a true hepatotoxicity which implies hepatocyte damage rather than a form of tolerance. It is important to remark that we ruled out other causes that might have explained the liver injury as well as alcohol or hepatotoxic drugs intake, but we should be aware that the patient could be hiding the consumption of illegal drugs or herbal remedies [45]. In their study Paul *et al.* reported that ATI levels were associated with loss of response to infliximab. The ELISA used in their study was able to assess ATI levels independently from IFX trough concentrations. This may partly explain the discrepancy between our results and previous reports [46, 47]. Immunomonitoring has been increasingly recognized as a useful tool to explore the immune basis behind LOR to anti-TNF-α therapy. It can be used alongside other biochemical predictors of LOR such as CRP and faecal calprotectin [48]. In their one retrospective study Tighe *et al.* 2017 analysed patients who previously had stand-alone anti-TNF-α trough and antibodies measured [38]. They aimed to find out whether these stand-alone anti-TNF-α trough and antibody levels would be useful in predicting future outcomes [38]. Similar to other studies, a significant number of their cohort treated with anti-TNF-α had a negative outcome (27%, 20/74) [14, 49] it is important to note that we ruled out other causes that might have explained the liver injury as well as alcohol or hepatotoxic drugs intake, but we should be aware that the patient could be hiding the consumption of illegal drugs or herbal remedies [50]. It is worth noting some considerations related to the clinical course of thiopurine-induced liver injury. First, it is important to point out that a small percentage of patients, less than 5%, presented with a slight elevation of LFTs that did not have clinical implications: the abnormalities in liver chemical tests returned to normal values during the follow-up and it was not necessary to adjust the dose of immunomodulator [51]. As with other drugs, thiopurine-induced liver injury occurred more frequently within the first months of treatment, 50% of cases within the first 3 months [52]. Moreover, treatment withdrawal because of hepatotoxicity occurred in most cases, 75%, during this period of time [53]. Despite this, in some cases the liver injury was only detected after a long period of follow-up leading to therapy withdrawal [54]. This finding is surprising because the long delay makes the role of the suspected drug unlikely; the explanation of this event could be related to a cumulative effect of the metabolites on the liver or to the confluence of multiple factors that could be triggers of an autoimmune liver injury. We found acute hepatocellular hepatitis in 87% of patients, in contrast with previous descriptions that considered pure cholestasis as the typical pattern [55]. In all cases LFTs returned to normal values and no chronic disease was detected [56]. When hepatotoxicity occurred, the treatment was withdrawn in 31% of patients, but an important percentage, forty four, was able to continue on the full dose of thiopurine once the dose was temporarily adjusted [57]. This group of patients had a dose-dependent hepatotoxicity rather than an immunoallergic hepatitis [58]. The rationale about how these patients were able to return to full doses of thiopurinic immunomodulators may be theoretically explained by the confluence of multiple factors in the onset of hepatotoxicity: dose of immunomodulator, concomitant treatment, quality of nutrition, drug interaction, etc. [59]. Schnitzler *et al.* 2009 postulated that the variation in injury pattern could be secondary to variables such as concomitant medications or dosage of medications [60]. Dosage of TNF-α antagonists did not correlate with liver injury in our case series [61]. Amongst our patients, Subject 1 received therapy with high dose infliximab (10 mg/kg every 8 weeks) when hepatotoxicity was documented. However, Subjects 2 and 3 received standard doses of infliximab (5 mg/kg every 8 weeks) and standard induction dosing of adalimumab (160 mg at week 0, 80 mg at week 2, and 40 mg every other week thereafter), respectively, when liver injury was noticed. Latency time to the development of liver toxicity was also variable. In some cases, liver toxicity developed after eighteen months of infliximab, whereas toxicity

developed within 3 months in some cases [62]. Hepatotoxicity was not related to any particular TNF-α antagonist, and patient age also varied among our 3 patients [63]. The variability of histology, dosage, time to toxicity, and presence of concomitant medications, in our patients as well as in the review of published cases, highlights the idiosyncratic nature of this drug-induced liver injury [1]. As clinician awareness of this entity increases, and more cases are detected, hopefully distinct patterns of injury will be delineated so that early detection can take place and fulminant liver failure can be prevented [64].

In conclusion, this study summed up the broad information on occurrence of biologic-related hepatotoxicity in IBD patients in the clinical practice setting.

Quality of the evidence

Two of the included studies were judged to be at low risk of bias [38, 40]. Four studies were rated at unclear risk of bias for random sequence generation and allocation concealment [33, 35, 38, 60]. Two studies were at unclear risk of bias for blinding [33, 36] and one study was at unclear risk of bias for incomplete outcome data [39].

Potential biases in the review process

A comprehensive literature review was conducted to help ensure that we included all relevant studies. Two review authors independently assessed for study inclusion, extracted data and assessed for risks of bias. The main limitation of this review is the lack of data available for endoscopic and histological end points.

Conflict of interest

The authors declare no conflict of interest.

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