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Hepatotoxicity Associated with the Use of Anti-TNF-α Agents

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Abstract

Medications to inhibit the actions of tumour necrosis factor alpha have revolutionized the treatment of several pro-inflammatory autoimmune conditions. Despite their many benefits, several serious side effects exist and adverse reactions do occur from these medications. While many of the medications' potential adverse effects were anticipated and recognized in clinical trials prior to drug approval, several more rare adverse reactions were recorded in the literature as the popularity, availability and distribution of these medications grew. Of these potential adverse reactions, liver injury, although uncommon, has been observed in some patients. As case reports accrued over time and ultimately case series developed, the link became better established between this family of medicines and various patterns of liver injury. Interestingly, it appears that the majority of cases exhibit an autoimmune hepatitis profile both in serological markers of autoimmune liver disease and in classic autoimmune features seen on hepatic histopathology. Despite the growing evidence of this relationship, the pathogenesis of this reaction remains incompletely understood, but it appears to depend on characteristics of the medications and the genetic composition of the patients; it is likely more complicated than a simple medication class effect. Because of this still incomplete understanding and the infrequency of the occurrence, treatments have also been limited, although it is clear that most patients improve with cessation of the offending agent and, in certain cases, glucocorticoid use. However, more needs to be done in the future to unveil the underlying mechanisms of this adverse reaction.

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Compliance with Ethical Standards

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1 Introduction

Tumour necrosis factor alpha (TNF-α) was discovered in 1975 as a protein with a molecular weight of 26 kDa, produced by lymphocytes and macrophages, which is expressed on the plasma membrane [1–3]. There, its extracellular domain can be cleaved by matrix metallo-proteinases, which result in release of a soluble 17 kDa form (sTNF-α) [4]. Both membrane-bound TNF-α (mTNF-α) and sTNF-α forms are active in their trimeric forms, and the two forms of TNF may have distinct biological activities. TNF-α is part of a large family of proteins with diverse inflammatory, proliferative, apoptotic and antitumoral effects [4]. Members of the TNF-α superfamily have both beneficial and potentially harmful effects. Although TNF-α, for example, has been linked with physiological proliferation and differentiation of B cells under steady-state conditions, it also has been linked with a wide variety of diseases, including autoimmune disorders [4].

TNF-α can be either pro- or anti-inflammatory, depending on whether it acts on an effector (e.g. macro-phage) or a target (e.g. endothelial) cell, releasing ligand or receptors, respectively. The activation of TNF-α receptor (TNF-R) is associated with an acute phase reaction, fever, apoptosis and anti-tumour activity [4, 5]. TNF-α is not usually detectable in the serum of healthy individuals, but elevated serum and tissue levels are found in many inflammatory and infectious conditions, and serum levels correlate with the severity of infections [3].

Inhibitors of TNF-α were developed in the 1990s, and the first ones, infliximab and etanercept, were approved by the US Food and Drug Administration (FDA) in 1998 for the treatment of Crohn's disease and rheumatoid arthritis (RA), respectively [5, 6]. Thereafter, adalimumab was approved in 2002 for RA, certolizumab in 2008 for RA, and golimumab in 2009 for RA, psoriatic arthritis and ankylosing spondylitis [6].

Many patients with the above inflammatory conditions are now taking anti-TNF-α medications on an ongoing basis, as these biological response modifiers are widely prescribed to modify the body's response to inflammation. Sales of anti-TNF-α agents in the USA alone topped US$10 billion in 2010 [4]. Initially, adverse events (AEs) associated with the use of anti-TNF-α molecules focused on autoimmune features and injection site reactions, whereas liver injury was not emphasized in the original labels (Table 1). However, an FDA postmarketing surveillance programme received more than 130 reports of liver injury resulting from either infliximab or etanercept treatment within 5 years [7]. These reports have been extended, and the liver injury due to these agents has been better characterized in terms of clinical and histological presentation in the more recent literature [8]. Currently, all of the TNF-α antagonists have been associated with drug-induced liver injury (DILI) [8]. In addition, these agents carry specific warnings about the risk of reactivation of chronic hepatitis B and risks of tuberculosis (TB) and other infections [9]. TNF-α inhibitors increase susceptibility to new infections or reactivation of concurrent or incident infections. Thus, before their use for therapy, screening for TB [with chest radiography and an interferon-gamma (IFN-γ) release assay] and certain viral infections (such as hepatitis B virus, hepatitis C virus, cytomegalovirus and herpes virus) is recommended [10].

Two cases of successful treatment with etanercept without recurrent DILI, following a prior DILI episode attributed to infliximab, have recently been reported, suggesting that cross-toxicity or a 'class effect' is not universal among the different TNF-α antagonists in all patients [11, 12]. However, it has been shown that several TNF-α antagonists have a similar ability to elicit the development of serological markers of autoimmunity [8]. These compounds have also been associated with reactivation of latent TB, hepatitis B, and development of lymphoma, autoantibodies and skin reactions [10].

The purpose of this paper is to review the types, typical clinical features, management and prognosis of DILI associated with anti-TNF-α medications.

2 Literature Search

A literature search was conducted in PubMed to identify published articles relevant to our focus on adverse reactions to anti-TNF-α agents, with a particular concentration on liver injury. Articles published from 1988 through June 2015 were included. The search terms used were combinations of the following terms: 'anti-tumour necrosis factor', 'drug-induced liver injury', 'infliximab', 'etanercept', 'adalimumab', 'certolizumab' and 'golimumab'. Articles were reviewed and selected on the basis of relevance to our subject matter, and the selected articles were reviewed. Articles that were deemed relevant were read and scrutinized in detail. Articles were not excluded on the basis of the language in which the article was printed, and all articles printed in languages other than English were appropriately translated. Articles were excluded if it was felt that the information provided in the article was insufficient to conclude that the patient had a drug injury from an anti-TNF-α medication. Similarly, data that emerged from clinical trials were not included, because of the relative paucity of early data on liver injury until individual case reports started to emerge. Weight was given to larger case series (n >4), but small case series and individual case reports were also reviewed and included. The first large literature case review was by Ghabril et al. [8], in 2013, which included 28 cases from the literature and six cases from the US Drug-Induced Liver Injury Network (DILIN). Since the publication by Ghabril et al., our search uncovered 11 additional case reports and five case series that have been published and are reviewed here. The combined cases from these additional reports add 86 new cases that had not yet been reported when the review by Ghabril et al. was written.

3 Reported Adverse Effects: Focus on DILI

While anti-TNF-α medications are generally considered to be well tolerated, several significant adverse effects have been described. In the current manufacturers' prescribing information for infliximab, etanercept, adalimumab, certolizumab and golimumab, several warnings and adverse reactions are listed, including the risk of serious infection, malignancies, reactivation of hepatitis B, demyelinating disease of the central nervous system, pancytopenia, worsening heart failure and triggering of autoimmune disease, especially a lupus-like syndrome [13–17]. Therefore, many of the most significant adverse effects of the medications appear to be a class effect related to the ability of these agents to block the effects of TNF-α. As with most medications, after several years of use, other postmarketing adverse reactions were reported. Examples of some of these adverse effects

associated with various anti-TNF-α medications have included psoriasis, vasculitis, various dermatological reactions, sarcoidosis and ocular reactions [18–20]. That being said, these adverse reactions are relatively rare and have occurred in small numbers of subjects, usually described in individual case reports. However, there were some postmarketing adverse reaction reports of liver injury associated with use of anti-TNF-α medications, which, while uncommon, were nonetheless significant [8, 21].

In the initial reports of liver injury associated with infliximab and etanercept that appeared in the FDA post-marketing surveillance programme, several other confounding factors or potential other sources of liver injury were found. However, it was noted in seven cases that there was a strong association with anti-TNF-α medication use [22]. Case reports also emerged in the published literature, describing various types of liver injury, including both hepatocellular and cholestatic injury patterns associated with anti-TNF-α medications [22–25]. As the indications for the anti-TNF-α class of medications expanded and usage became more widespread, case series were collected, further providing evidence that there was an association between TNF-α antagonists and liver injury [26]. Over the past few years, several larger studies—including queries of large databases of patients on anti-TNF-α therapy and liver injury networks—have been published, and these have helped to better characterize the liver injury patterns that are encountered [8, 27–29].

As already mentioned, Ghabril et al. [8] described 34 cases of DILI attributed to anti-TNF-α medications. Six of these cases were obtained from the DILIN database, and 28 were obtained from literature review. The method of causality assignment used by the US DILIN was utilized to assign probability [30, 31]. Roussel-Uclaf Causality Assessment Method (RUCAM) scores also were developed. On the basis of the analysis, 34 cases of DILI were found in which anti-TNF-α medications were at least the probable cause of the liver injury, and they were found to be the likely cause in the majority (21/34) of the cases [8].

Another recent study by Björnsson et al. [27] described 11 cases of liver injury that were identified at the National University Hospital of Iceland (Reykjavík, Iceland). Again, the RUCAM was used to assign causality, and in the 11 cases described, the anti-TNF-α medications were felt to be causative. In the majority (8/11) of the cases, the authors felt it was highly probable that the liver injury was due to the anti-TNF-α medications [27]. Similarly, a recent paper by Shelton et al. [29] reported a retrospective cohort review of patients from two large academic medical centres and their affiliated clinics. These authors found 102 cases of elevated serum alanine aminotransferase levels in patients with inflammatory bowel disease on anti-TNF-α therapy, of which 48 were felt to be due to anti-TNF-α therapy, based on RUCAM analysis (Table 2) [29].

When the studies by Ghabril et al. [8], Björnsson et al. [27] and Shelton et al. [29] are compared, there are some notable differences, including (inter alia) the definition of liver injury and the patient populations studied (Fig. 1a). However, there also are several prominent similarities that allow for a better understanding of the nature of the liver injury caused by anti-TNF-α medications. First, it appears that the anti-TNF-α medication that most commonly causes liver injury is infliximab [8, 27, 29], whereas etanercept and adalimumab have been implicated to much lesser degrees (Fig. 1a) [8, 27, 29]. These three

anti-TNF-α agents are also the agents that have been prescribed for longer periods and thus have been available for a longer duration of use when compared with the newer medications in the class. Prescription trends and DILI risks are discussed below.

Second, while there are cholestatic and hepatocellular patterns of liver injury reported in the cases described by Ghabril et al. [8], Björnsson et al. [27] and Shelton et al. [29], the predominant form seen is a hepatocellular type of liver injury with features of autoimmunity [32]. Similarly, in other published cases, there are varying types of liver injury reported, but the majority show autoimmune features, such as autoimmune patterns of injury found on liver biopsy (many plasma cells, pseudo-rosettes of hepatocytes, etc.) and positive serological markers, including high titres of antinuclear antibodies and anti–smooth muscle antibodies [23, 25, 33–35].

Furthermore, Rodrigues et al. [36] recently described eight cases of an autoimmune pattern of liver injury, many relatively mild in severity, based on biopsy and serological data attributed to anti-TNF-α therapy (Table 2).

Interestingly, while all of the anti-TNF-α medications share similar adverse effect profiles, and multiple anti-TNF-α agents have been associated with liver injury, it does appear that there is more than just a class effect phenomenon at work, because some patients have tolerated anti-TNF-α medications without adverse effects after developing a liver injury from a different agent in the class [8, 11, 12, 27, 37–39]. Interestingly, there has also been a report of a patient developing an autoimmune type of liver injury from infliximab and, after recovery, being retreated with infliximab once again without recurrence of the liver injury [36]. Until the mechanism of liver injury induced by the anti-TNF-α class of medications is fully elucidated, it will be difficult to understand the presence or absence of cross-reactions among medications within this class, or even the risk of repeated use of the same agent after anti-TNF-α liver injury has occurred in a patient. It remains unclear if anti-TNF agents actually precipitate de novo autoimmune hepatitis (AIH), which can relapse without precipitants in the absence of immunosuppression. The majority of reported experiences indicate a phenotype of DILI with autoimmune features, without relapses even after tapering of relatively short-term steroid therapy, when used. In addition, two reported cases of infliximab-related DILI with autoimmune features are instructive: in one instance, injury due to the drug developed in the postpartum period in a patient who had tolerated infliximab since before the pregnancy. This is consistent with an increased risk of development of AIH occurring in that period [40]. The persistence of serum aminotransferase abnormalities in another patient, which normalized only after a year of steroid therapy, with continued immunosuppression thereafter, argue against a self-limited injury and for an immunosuppression-responsive AIH [41].

Extra-intestinal manifestations of inflammatory bowel diseases, including primary sclerosing cholangitis, are well recognized, and patients with these (and other) disorders often are treated with other potentially hepatotoxic agents in addition to anti-TNF-α agents —for example, methotrexate and sulfasalazine [42]. Thus, assessment of causality of liver disease in such patients requires thoroughness and care, such as the detailed Delphic method adopted by the US DILIN [30, 31]. As already described, the clinical, laboratory and

histopathological features of DILI due to anti-TNF-α agents are usually those of hepatitis with autoimmune features, not those of cholestatic-type hepatitis, as occurs in primary sclerosing cholangitis. However, in cases of cholestatic-type hepatitis, which can be due to anti-TNF-α agents [8], it is important to assess the bile ducts with special care, with endoscopic or magnetic retrograde cholangiopancreatography, and perhaps liver biopsy.

The 'latency' (the time from the start of an anti-TNF-α drug to development of DILI) is variable. Ghabril et al. [8] found within their series of patients that the median time to onset of liver injury after starting therapy with an anti-TNF-α medication was 16 weeks (range 2–52 weeks). Similarly, Björnsson et al. [27] and Shelton et al. [29] described medians of 14 weeks (range 4–104 weeks) and 18 weeks (range 2–87 weeks), respectively. Shelton et al. [29] focused their discussion and data on injury due to infliximab, and DILI due to this agent accounted for the vast majority (45/48 cases) of the patients in their series.

Ghabril et al. [8] noted that anti-TNF-α DILI with an autoimmune phenotype (22 cases) was associated with a somewhat longer median latency of 16 weeks, compared with 10 weeks in cases without autoimmune features (12 cases). These data would suggest that the majority of incidents of liver injury that occur secondarily to anti-TNF-α therapy occur within the first 20 weeks of therapy (Table 2). However, Rodrigues et al. [36] noted a mean onset of liver injury after eight doses of anti-TNF-α therapy in their series of eight patients, which would be a longer latency of approximately 46 weeks, assuming standard loading and dosing of infliximab. Long latencies (up to ~156 weeks) also were recently described by Rösner et al [43]. Thus, data from the aforementioned series and published individual case reports demonstrate considerable variability in the latency to onset of liver injury after the start of anti-TNF-α therapy, ranging from after only one dose to after more than 2 years of therapy [8, 27, 43, 44].

As outlined in Table 1, the majority of the cases of intrinsic liver injury associated with anti-TNF medications were noted in postmarketing reporting. In the current manufacturer prescribing information for infliximab, hepatotoxicity is clearly listed in the "Warning and Precautions" section as well as in the "Adverse Reactions" section [15]. The prescribing information for adalimumab, etanercept, golimumab and certolizumab lists "hepatotoxicity" or "elevated liver enzymes" in the "Postmarketing Experience" and/or "Adverse Reactions" sections [13–17]. On the basis of this growing body of evidence of anti-TNF induced liver injury, it seems appropriate that hepatotoxicity should be prominently listed in the manufacturer-supplied prescribing information.

3.1 Prescribing Trends and DILI Risk of Specific Anti-TNF-α Agents

The risk of DILI associated with specific anti-TNF-α agents has been difficult to estimate, because of [1] the selective nature of reporting of associated DILI via case reports or case series (i.e. an unknown numerator); and [2] the limited data on the number of prescriptions (i.e. an unknown denominator). If the risk of DILI were similar for all agents in this class, then the overwhelming preponderance of infliximab-related DILI in the literature would suggest that infliximab is by far the most prescribed anti-TNF-α agent in this class. However a US multi-institutional study indicated that, among 16,022 patients treated with anti-TNF-α agents between 1998 and 2007 (for rheumatological, dermatological and inflammatory

bowel disease), 4494 were receiving etanercept, 3906 were receiving infliximab and 2084 were receiving adalimumab [45]. Few data speak to trends in utilization regardless of underlying disease. A Stanford University clinical data repository analysis suggested that infliximab therapy for inflammatory bowel disease peaked at that centre in 2008, while adalimumab use has steadily increased since then [46], and we believe that patterns of use at our centres are similar. On the basis of Thomson-Reuters MarketScan® data reporting of anti-TNF-α prescriptions for RA, psoriasis, psoriatic arthritis or ankylosing spondylitis between 2005 and 2009, the most frequently used agent was etanercept (in 12,065 patients, with annual costs of US$15,836 per patient), followed by adalimumab (in 5685 patients, with annual costs of US$19,457 per patient), followed by infliximab (in 3902 patients, with annual costs of US$24,018 per patient) [47]. A more recent report on non-discounted spending on medicine in the USA annually between 2009 and 2013 indicates that the greatest increase in expenditure over this period was for adalimumab (a 124 % increase to US$5.6 billion), followed by etanercept (a 27 % increase to US$4.7 billion) and infliximab (a 28 % increase to US$4.1 billion) [48]. A similar report ranked adalimumab and etanercept as first and second among the top ten medicines by expenditure (infliximab was not on the list) [49]. Together, these data suggest that infliximab currently is not prescribed more commonly than adalimumab or etanercept. Therefore, the more frequent reporting of infliximab-related DILI probably reflects a higher risk of DILI with this agent compared with others in its class. This is supported by the findings of an Icelandic population-based study, which indicated DILI risks of 1 in 120 with infliximab, 1 in 270 with adalimumab and 1 in 430 with etanercept therapy [27]. A search of the US Adverse Event Reporting System (AERS) Spider (http://www.chemoprofiling.org/AERS) was performed. This system generates summaries of specific reported AEs with specific drugs [50]. Searches using the anti-TNF-α agent names indicated 18,893 reported AEs with infliximab, 45,522 with adalimumab, 30,056 with etanercept, 4225 with certolizumab and 779 with golimumab. Of these, AIH was reported in 29 instances with infliximab but was not reported with the other agents. There were no other reported liver-specific AEs that could represent potential DILI.

3.2 Prevention, Management and Outcomes of DILI Due to Anti-TNF-α Agents

While the causative relationship between the anti-TNF-α family of medications and liver injury is becoming clearer, there remain few reliable data to help guide treatment for DILI due to these agents. Of greatest importance, of course, is to stop the offending anti-TNF-α medication immediately. In some cases, corticosteroids were administered with good results, whether used initially or after failure of serum aminotransferase levels to normalize after the anti-TNF-α agent was stopped [8, 23–27, 29, 40, 43]. Unfortunately, there is currently not an evidence-based treatment strategy that would help clinicians decide which patients would benefit most from steroid therapy or guide the duration of therapy. However, in the vast majority of the available cases available for review, it appears that the liver injury ultimately improves, and while steroid therapy seems to provide some benefit in certain situations, whether corticosteroids are truly of benefit or not remains unclear [8, 23–27, 29, 40, 43]. There is appropriate concern regarding the use of corticosteroids in patients who are already immunosuppressed because of recent administration of anti-TNF-α agents, which are well known to increase risks of infections, as already described. Then, too, corticosteroids have several other known adverse effects of their own, including weight gain, systemic arterial

hypertension, development of hyperglycaemia/diabetes mellitus and alterations of mood. However, the risks of such adverse effects may be decreased by use of budesonide rather than pred-nis[ol]one, and by limiting the duration of corticosteroid therapy as far as possible.

It has also been recently suggested that concomitant use of disease-modifying anti-rheumatic drugs (DMARDs)—typically, anti-inflammatory/immunomodulatory agents—may prevent liver injury caused by anti-anti-TNF-α drugs. In a recent retrospective study, Björnsson et al. [27] reported that among 33 patients treated with anti-TNF-α agents, those concomitantly treated with methotrexate or other DMARDs were less likely to develop DILI.

3.3 Postulated Mechanisms of Pathogenesis of DILI Due to Anti-TNF Agents

Liver enzyme abnormalities can be observed in patients with RA, inflammatory bowel disease or psoriasis treated with TNF-α inhibitors. Underlying morbidity, such as viral hepatitis or non-alcoholic fatty liver disease, has been implicated in such cases contemporaneously with the use of anti-rheumatic and anti-inflammatory drugs with established hepatic toxicity [51]. As already described, cases of AIH with concomitant liver enzyme abnormalities and circulating antinuclear antibodies [and/or elevated immunoglobulin G (IgG) levels] caused by anti-TNF-α have similarly been reported [52]. Differentiating AIH from anti-TNF-α-induced DILI is challenging, as both conditions may present with similar laboratory and histological features. To date, differential diagnosis has been based most firmly on the absence of AIH relapse after the resolution of liver injury with or without immunosuppressive therapy and with continuing non-use of the implicated anti-TNF-α drug [53]. The great majority of patients with idiopathic AIH will experience relapses when systemic corticosteroid therapy or other immunosuppressive therapy is discontinued.

TNF-α is a potent inflammatory cytokine, mainly expressed by monocytes/macrophages, T cells and natural killer (NK) cells, all of which are either resident or infiltrating hepatic leukocytes [54], as well as endothelial cells. TNF-α is initially expressed as its membrane-bound precursor (mTNF-α) cleaved by the TNF-converting enzyme metalloprotease [also known as ADAM 17 endopeptidase; Enzyme Commission (EC) number 3.4.24.86] and released in a soluble form (sTNF-α). sTNF-α is biologically active through autocrine and paracrine signalling mediated by TNF-R1 and TNF-R2, which are ubiquitously expressed by nucleated cells [55]. mTNF-α can act both as a ligand, signalling mainly through TNF-R2 (and, to a lesser extent, TNF-R1), and as a receptor through reverse signalling in mTNF-α-expressing/TNF-α-producing cells [56].

Potential mechanisms of the pathogenesis of DILI caused by anti-TNF-α agents vary on the basis of the structure, functional properties and biological activities of the aforementioned agents (Table 3). As an example of structural differences among anti-TNF-α agents, infliximab—the only chimeric mouse–human monoclonal antibody (others are fully human)—is also the most prone to cause liver injury, as already described. In vitro studies with humanized mouse IgG have shown that the three complementarity-determining variable regions of both heavy and light segments can elicit CD4+ T cell responses associated with numerous human leukocyte antigen (HLA) class II alleles [57]. Although immunogenicity of those complementarity-determining regions remains minimal, it is tempting to speculate

that this region may be more important in pathogenesis of DILI in subjects with specific HLA types, and this helps to account for why DILI occurs in only a few patients treated with anti-TNF agents.

From a functional standpoint, binding and neutralizing of sTNF-α is a common feature of anti-TNF-α agents, but the several available drugs exert differential effects on mTNF-α. Disruption of liver homeostasis by blocking of sTNF-α can promote hepatocyte apoptosis and prevent liver regeneration in a transgenic mouse model of chronic hepatitis C infection [58]. This adverse reaction to sTNF-α blocking in the liver originates from the ambivalent biological activity of the cytokine. For example, sTNF-α promotes caspase 8 activation and apoptosis; yet, at the same time, it mitigates cell death by promoting NF-κB activation and cell proliferation [59].

Two key differences among anti-TNF-α agents' biological activities are their opsonizing activity and/or ability to trigger reverse signalling. All FDA-approved anti-TNF-α agents containing a human IgG fragment crystallizable (Fc) portion (infliximab, etanercept, adalimumab and golimumab) can promote antibody-dependent cell-mediated cell death (ADCC) of mTNF-α/TNF-α-producing cells (Table 3). The same anti-TNF-α agents promote mTNF-α reverse signalling. While not specific only to liver biology, mTNF-α reverse signalling has been associated with E-selectin expression, IFN-γ production by T cells and alloresponse against endothelial cells [55]. mTNF-α reverse signalling can also trigger a pro-inflammatory signal—including, for instance, TNF-α production by monocytes/macrophages and NK cytotoxicity (upregulation of perforin, granzyme B expression) [56].

While the aforementioned adverse biological effects of anti-TNF-α agents (hepatocyte apoptosis, ADCC, pro-inflammatory reverse signalling) have been demonstrated either clinically or using experimental models, the direct link between anti-TNF-α agents and liver damage remains controversial. Liver damage may indeed be caused by a combination of underlying autoimmune diathesis in patients treated with anti-TNF-α agents with potential adverse—as well as favourable—biological effects.

4 Conclusion

There is an apparent causative link between anti-TNF-α therapy and liver injury and, while the incidence of this AE appears to be relatively low (given the few reports in the literature compared with the large number of patients receiving the medications), the liver injury is nonetheless significant. In many cases, the liver injury that is sustained appears to have an autoimmune pattern, but little is understood about the pathophysiology of this reaction. Furthermore, even less is understood regarding the appropriate treatment when this type of liver injury does occur. Future studies are needed to further define the mechanism of liver injury secondary to anti-TNF-α medications and the optimal role of corticosteroids in this patient population after liver injury develops. However, given the relative rarity of such reactions, meaningful data to achieve this aim will prove difficult to obtain. Another goal is to develop reliable predictors of the risk of DILI due to these agents, so that, in future, the development of this adverse effect is avoided.

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Key Points

Drug-induced liver injury (DILI) associated with anti-tumour necrosis factor alpha (anti-TNF-α) agents is uncommon but can occur with a wide range of latency ranging from a single dose to over 2 years of treatment.

Anti-TNF-α-associated DILI is commonly characterized by autoimmune serological and histological features, and responds well to glucocorticoids, with very low rates of recurrent autoimmune injury after resolution.

DILI associated with one anti-TNF-α agent has been reported to recur with the use of an alternative anti-TNF-α agent after recovery; therefore, close monitoring is recommended in these scenarios.

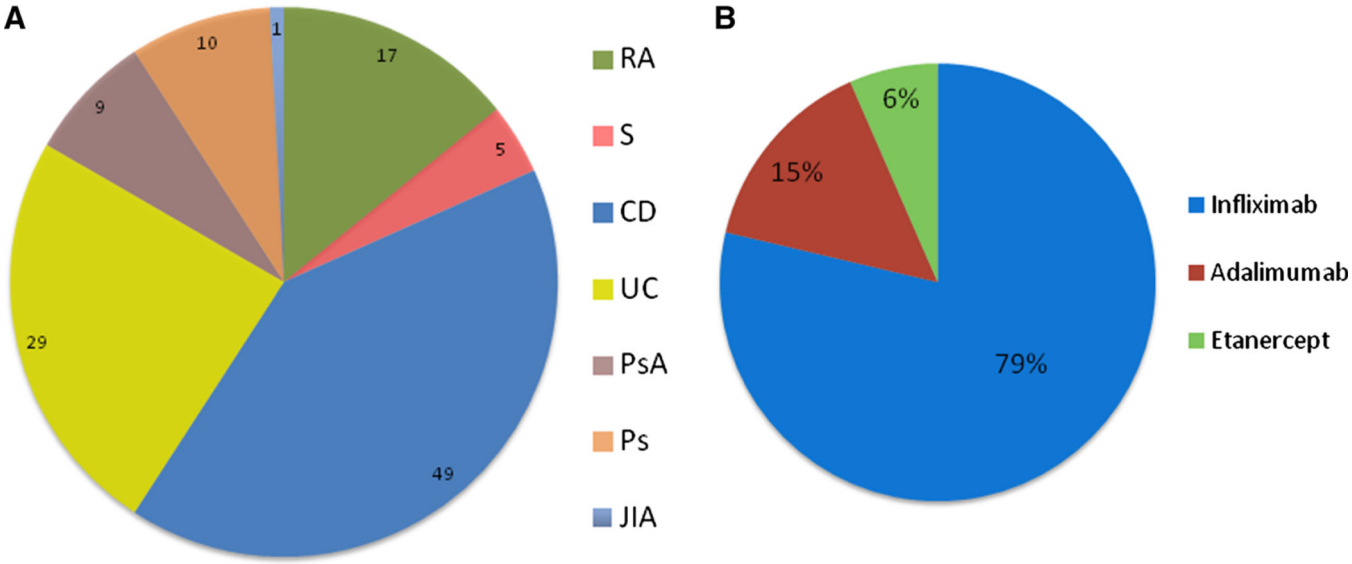

Fig. 1.

a Indications for use of anti-tumour necrosis factor alpha (anti-TNF-α) agents among subjects who developed drug-induced liver injury (DILI): reported underlying conditions of the patients who developed liver injury secondarily to anti-TNF therapy. The *numbers* of subjects in each category are displayed on the chart. *CD* Crohn's disease, *JIA* juvenile inflammatory arthritis, *Ps* psoriasis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *S* spondylitis, *UC* ulcerative colitis. **b** Anti-TNF-α medications cited in the cases as the cause of liver injury, represented as percentages of the total cases presented (note: in the reports by Titos-Arcos et al. [39] and Rösner et al. [43], a patient from each report had two separate incidents of liver injury due to both adalimumab and etanercept, and both are counted in this figure)

Table 1

Main adverse events noted in the US Food and Drug Administration (FDA)-approved original labels of anti-tumour necrosis factor (anti-TNF) agents

Name	Year of FDA approval	Injection site reaction	Autoantibodies	Upper respiratory infection	Other	Hepatobiliary
Infliximab	1998	Yes	Yes	Yes	Nausea, pain, fatigue	Elevated liver enzymes
Etanercept	1998	Yes	Yes	Yes	Headache	Cholecystitis
Adalimumab	2002	Yes	Yes	Yes	Lymphoma, rash	Serum alkaline phosphatase increase in 5 %, cholecystitis, hepatic necrosis
Certolizumab pegol	2008	Yes	No	Yes	Arthralgias	Elevated liver enzymes
Golimumab	2009	Yes	Yes	No	–	Serum alanine aminotransferase ≥3× upper limit of normal in 2 % (same as placebo), severe hepatic reactions

Table 2

Selected data from case series and single case reports

Study	Cases of DILI [*n*]	Female subjects [*n* (%)]	Mean age [years]	Cases due to infliximab/ other anti-TNF agents (*n*/*n*)	Autoimmune features[c] (positive/ tested) (*n*/*N*)	Latency [median time from start to onset of DILI]	Cases treated with steroids (*n*)	Cases where DILI was resolved (*n*)
Ghabril et al. [8]	34[a]	22 (65)	41	26/8	22/34	16 weeks	12	33[i]
Björnsson et al. [27]	11	8 (73)	46	9/2	8/11[d]	14 weeks	5	8[j]
Shelton et al. [29]	48	21 (44)	32	45/3	24/26	18 weeks	4	41
Rodrigues et al. [36]	8	5 (63)	46	7/1	8/8	8 doses	8	6[k]
Parekh et al. [26]	3	3 (100)	34	2/1	0/3	12 weeks	0	3
Carvalheiro et al. [60]	1	0 (0)	24	1/0	0/1	2 doses	0	1
Colina et al. [41]	1	1 (100)	52	1/0	1/1	4 doses	1	1
Kim et al. [32]	1	1 (100)	39	0/1	0/1	28 weeks	0	1
Cheng et al. [44]	1	0 (0)	27	1/0	0/1	1 dose	1[h]	1
van Casteren-Messidoro et al. [40]	2	2 (100)	38	2/0	2/2	Case 1: 3 doses; case 2: 2 years[f]	2	2
Titos-Arcos et al. [39]	1	1 (100)	47	0/1	1/1	2 years[g]	0	1
Grasland et al. [37]	1	1 (100)	35	0/1	1/1	5 doses	1	1
Perdan-Permajar et al. [38]	2	0 (0)	42	0/2	0/2[e]	12 weeks	0	2[h]
Dang et al. [61]	1	1 (100)	47	1/0	1/1	3 doses	1	1
Kinnunen et al. [62]	1	1 (100)	46	1/0	0/1	2 doses	0	0
Frider et al. [63]	1	0 (0)	35	0/1	0/1	12 weeks	0	0
Rösner et al. [43]	3	Not stated	43	1[b]	3/3	Variable, up to ~156 weeks	3	3[l]

anti-TNF anti-tumour necrosis factor, *DILI* drug-induced liver injury, *DILIN* Drug-Induced Liver Injury Network

[a] Six cases from the DILIN and 24 from the literature

[b] Mild DILI due to infliximab; more marked and severe after etanercept and adalimumab

[c] Patients were described as having positive autoimmune serology (either antinuclear antibodies or anti–smooth muscle antibodies) or evidence of autoimmune features on liver biopsy; if serological data and liver biopsy data differed, then preference was given to biopsy data

[d] Three of the eight patients had positive antinuclear antibodies prior to anti-TNF-α therapy; five liver biopsies were obtained, but it was not clear which patients had biopsies or not, so liver biopsy data were excluded for this study

[e] One patient with rheumatoid arthritis had positive serology but a liver biopsy not consistent with autoimmune hepatitis

[f] This case occurred while the patient was pregnant

[g] This patient had DILI due to etanercept and later adalimumab; the time of onset included in the table is for the initial DILI, which was due to etanercept

[h] Patients were already on steroids for underlying condition at the time of DILI

[i] One patient with underlying cirrhosis went on to receive a liver transplant

[j] At least one patient relapsed after withdrawal of steroids

[k] The other two cases were listed as "controlled on therapy"

[l] Case with repeated positive rechallenge with adalimumab

Table 3

Selected structural, functional and biological properties of anti-tumour necrosis factor alpha (anti-TNF-α) agents (adapted with permission from Sedger et al. [55])

Property	Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab
Structure	Chimeric mouse– human IgG1	Recombinant TNF-R2 with Fc portion of human IgG	Human IgG1	Humanized Peg Fab	Human IgG1
Half-life [days]	8–10	4	10–20	14	7–20
Functional and biological properties					
sTNF-α binding	Yes	Yes	Yes	Yes	Yes
Kd [pM]	44	11	127	90	18
sTNF-α neutralization	Yes	Yes	Yes	Yes	Yes
mTNF-α binding	2714	Yes	Yes	?	Yes
Kd [pM]	468	445	483		NA
mTNF-α reverse signalling	Yes	Yes	Yes	?	Yes
Fc-mediated ADCC	Yes	Yes	Yes	No	Yes

ADCC antibody-dependent cell-mediated cell death, *Fc* fragment crystallizable, *IgG* immunoglobulin G, *Kd* dissociation constant as relates to soluble and membrane-bound TNF-α receptor binding, *mTNF-α* membrane-bound tumour necrosis factor alpha, *Peg* pegylated, *sTNF-α* soluble tumour necrosis factor alpha, *TNF-R2* tumour necrosis factor alpha receptor 2, ? unknown