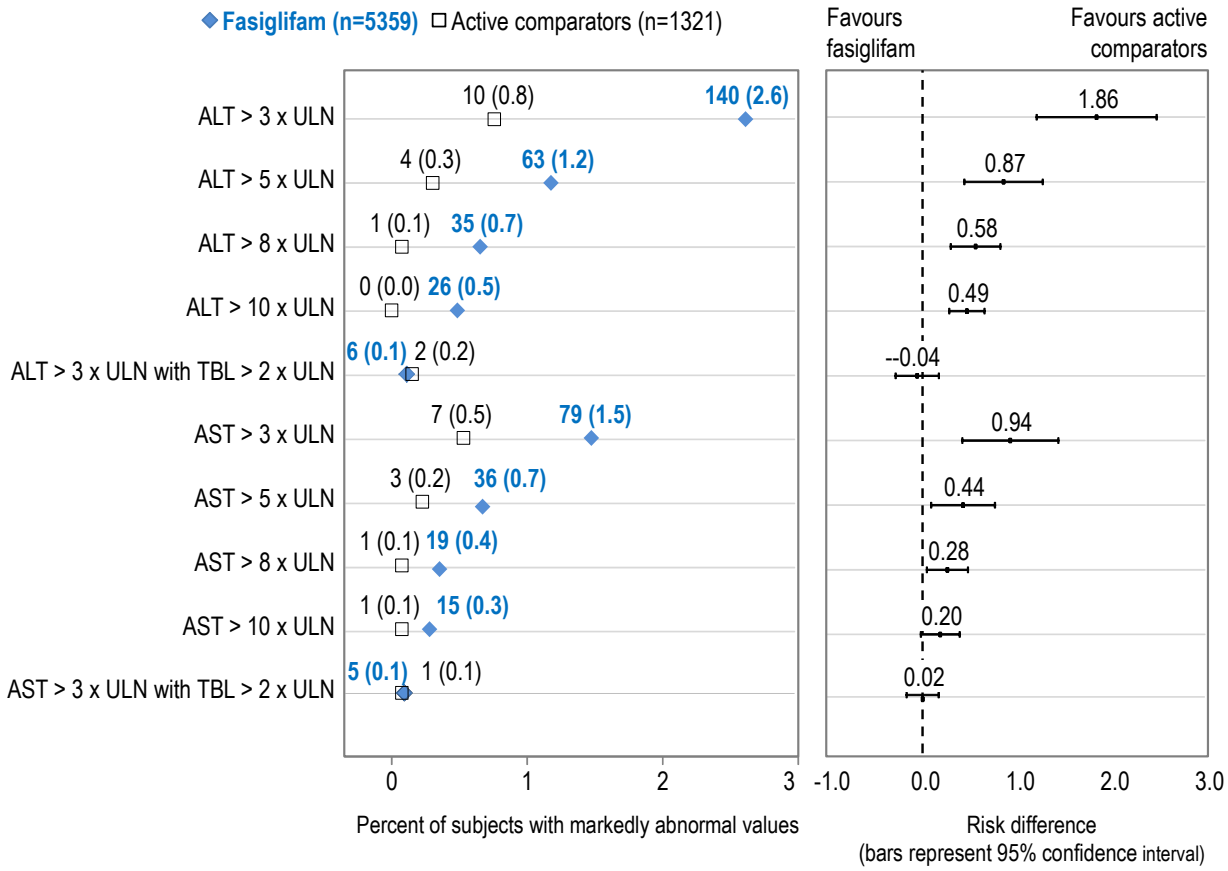
Drug-induced liver injury (DILI):
Current status and future directions for
drug development and the post-market setting

Supplemental Appendices

Updated 3 June 2020

APPENDIX 5. Data analysis for DILI assessment: Supplemental figures

Appendix 5, Figure 1. Risk plot

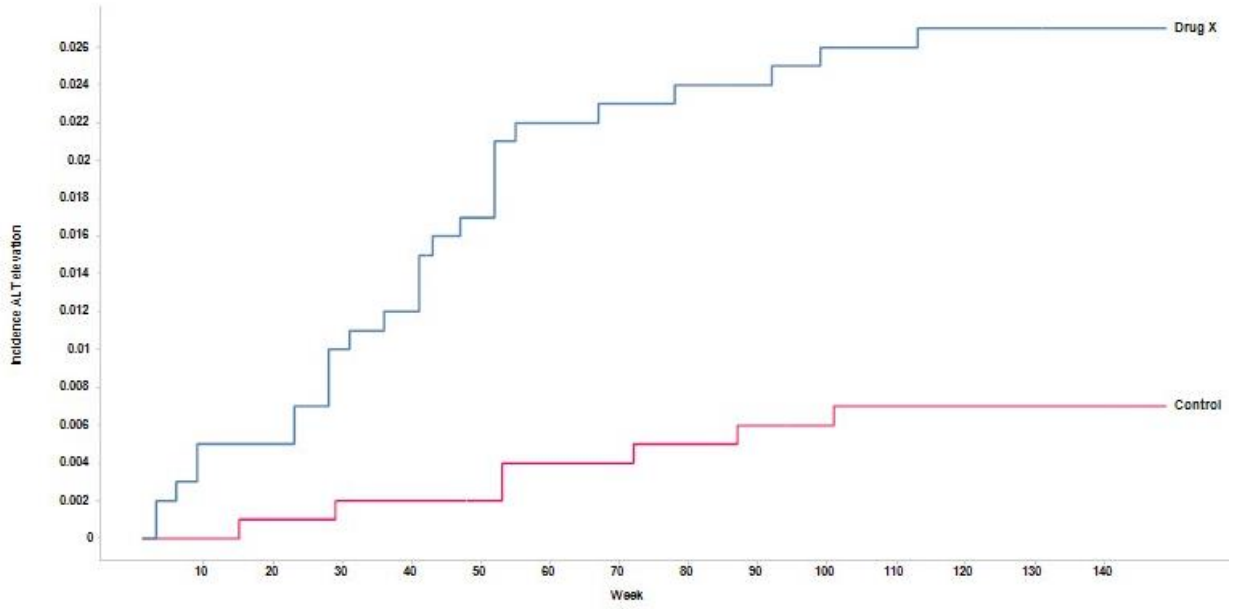


Supplemental Figure 1: Risk difference of markedly abnormal liver test values among fasiglifam, placebo, and active comparators for fasiglifam double blind controlled studies.

Based on numbers from reference [1].

The risk plot presents the risk difference between study drug and both placebo and active comparators [1] (only the study drug and the active comparator are shown here). The risk plot can highlight differences of liver test elevations between study drug and placebo or active comparator.

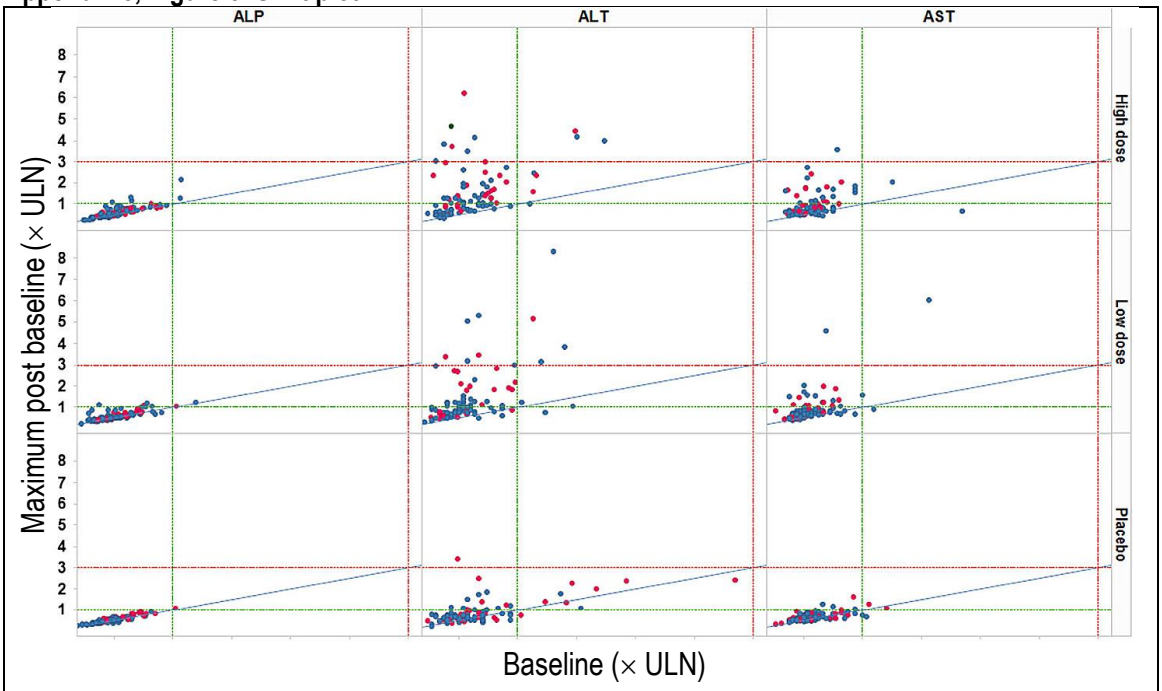
Appendix 5, Figure 2. Kaplan-Meyer plot



Supplemental Figure 2: Kaplan–Meier plot of incidence of ALT elevations over time across treatment groups
ALT alanine aminotransferase. From Merz M, Lee KR, Kullak-Ublick GA, et al. Methodology to Assess Clinical Liver Safety Data. Drug Saf (2014) 37 (Suppl 1): 33. https://dx.doi.org/10.1007%2Fs40264-014-0184-5. Published under license CC BY-NC 4.0. https://creativecommons.org/licenses/by-nc/4.0.

The Kaplan-Meier plot is a widely used graphical display that shows and compares time to event. Comparing time to elevation of liver test results across treatment groups is important in understanding and interpreting a liver safety signal as well as managing the risk associated with effects of study drug on the liver [2]. The common presentation for the Kaplan-Meier plot is the incidence of ALT elevations over time across treatment groups (**Supplemental Figure 2**). Identification of the window of susceptibility when ALT elevations occur by analysis of the Kaplan-Meier plot can provide important clinical information. For example, the most problematic idiosyncratic DILI occurs typically after 1-6 months of treatment [3].

Appendix 5, Figure 3. Shift plot



Supplemental Figure 3: Shifts from baseline, parameters by column, treatment groups by row, colour coding by gender

ALP=alkaline phosphatase, **ALT**=alanine aminotransferase, **AST**=aspartate aminotransferase, **ULN**=Upper limit of normal

Source: Merz M, Lee KR, Kullak-Ublick GA, Brueckner A, Watkins PB. Methodology to assess clinical liver safety data. Drug Saf. 2014;37(Suppl 1)S33–S45. Published under license CC BY-NC 4.0. https://creativecommons.org/licenses/by-nc/4.0.

The figure shows an example with four post-baseline observations per patient. Treatment groups are shown across rows and biomarker names across columns; colour coding is by gender. The blue diagonal line in each panel represents the line of identity, where the maximum post-baseline value equals the baseline value; points above the line represent increases and those below the line decreases from baseline. In addition, the plot allows to assess the number of patients exceeding certain threshold values, represented by the green (=ULN) and red (3xULN) horizontal and vertical dashed lines in each panel.

Appendix 5 – References

1 Marcinak JF, Munsaka MS, Watkins PB, *et al.* Liver Safety of Fasiglifam (TAK-875) in Patients with Type 2 Diabetes: Review of the Global Clinical Trial Experience. Drug Saf. 2018;41:625. (PubMed)

2 Merz M, Lee KR, Kullak-Ublick GA, Brueckner A, Watkins PB. Methodology to assess clinical liver safety data. Drug Saf. 2014;37(Suppl 1)S33–S45. (PMC full text, Journal full text)

3 Mosedale M, Watkins PB. Drug-induced liver injury: advances in mechanistic understanding that will inform risk management. Clin Pharmacol Ther. 2017;101:469–80. (PMC full text)

APPENDIX 6. Genetic susceptibility loci for DILI identified in GWAS and candidate gene studies

Sources: 4, 5, 6, 7

Association described: HLA allele	Drug studied	Study type & cohort population	Odds ratio
A*02:01 rs2523822 *TRNAI25*	amoxicillin-clavulanate	**GWAS:** 201 cases, 532 P controls *(European)*	2.3
A*30:02	amoxicillin-clavulanate	CGS: 75 cases, 885 P controls *(European)*	6.7
A*33:01	multiple	**GWAS:** 862 cases (21 terbinafine; 7 fenofibrate; 5 ticlopidine), 10588 P controls *(European)*	40.5; 58.7; 163.1
A*33:03 B*08	ticlopidine clometacin	CGS: 22 cases, 85 T controls *(Japanese)* CGS: 30 cases *(European)*	13
B*18:01	amoxicillin-clavulanate	CGS: 75 cases, 885 P controls *(European)*	2.9
B*35:02	minocycline	**GWAS:** 25 cases, 10588 P controls *(European)*	29.6
B*57:03	flucloxacillin	CGS: 197 cases, 6825 P controls *(European)*	79.2
B*57:01 rs2395029 *HCP5*	flucloxacillin	CGS: 51 cases, 282 P controls *(European)*	45
B*57:01	pazopanib	CGS: 429 cases, 1761 T controls	2.0
B*57:02	efavirenz + anti-TB	CGS: 46 cases, 46 controls *(African)*	8.1
B*57:03	efavirenz + anti-TB	CGS: 46 cases, 46 controls *(African)*	26.8
B*58:01	nevirapine	CGS: 57 cases, 111 T controls *(South African)*	
DQA1*01:02 protective	anti-TB	CGS: 56 cases, 209 T controls *(Indian)*	4
DRB1*15:01-DRB5*0101-DQB1*06:02; DQB1*06:02 rs9274407	amoxicillin-clavulanate	**GWAS:** 201 cases, 532 P controls *(European)*; CGS: *(European)* 35 cases, 300 P controls; 22 cases, 134 P controls; 40 cases, 140 P controls; 75 cases, 885 P controls	3.1
DRB1*07 *protective*[a]	amoxicillin-clavulanate	CGS: 40 cases, 140 P controls *(European)*	0.18
DRB1*07:	ximelagatran	**GWAS:** 74 cases, 130 T controls *(European)*	4.4
DRB1*15:01	lumiracoxib	GWAS 41 cases, 176 T controls *(International)*	5
DRB1*16:01-DQB1*05:02	flupirtine	**GWAS:** 614 cases (6 flupirtine), 10588 P controls *(European)*	18.7
DQB1*0201	anti-TB	CGS: 56 cases, 209 T controls *(Indian)*; **GWAS:** 59 cases, 111 T controls, 109 P controls *(Indian)*: association not confirmed	1.9

Association described: drug metabolism loci	Drug studied	Study type & cohort population	OR
ABCC2 rs717620	diclofenac	CGS: 24 cases, 48 T controls *(European)*	5
NAT2 slow acetylator alleles	isoniazid	CGS: 26 cases, 101 P controls *(European/Asian)*; **GWAS:** 24 cases - association not confirmed	4.25
UGT2B7*2	diclofenac	CGS: 24 cases, 48 T controls *(European)*; **GWAS:** 34 cases - association partly confirmed	8.5

Various other associations	Drug studied	Study type & cohort population	OR
ALG10B rs6582630	flucloxacillin	**GWAS:** 51 cases, 282 P controls *(European)*	2.8
C9orf82 (CAAP1) rs10812428	flucloxacillin	**GWAS:** 51 cases, 282 P controls *(European)*	2.9
ERN1 rs199650082	efavirenz	**GWAS:** 21 cases, 234 T controls *(African)*	18.2
FAM65B intron rs10946737	rifampicin	**GWAS:** 48 cases, 354 T controls; CGS: 27 cases, 217 T controls *(African)*;	3.4
lincRNA rs4842407	efavirenz + anti-TB	**GWAS:** 42 cases, 292 T controls *(African)*	5.4
MCTP2 rs4984390	flucloxacillin	**GWAS:** 51 cases, 282 P controls *(European)*	3.3
OR5H2 rs1497546	flucloxacillin	**GWAS:** 51 cases, 282 P controls *(European)*	6.6
PPARG rs17036170	multiple (diclofenac)	**GWAS:** 783 cases (30 diclofenac), 3001 P controls *(European)*	11.3
PTPN22 rs2476601	multiple	**GWAS:** 2048 cases, 12,429 P controls *(European, African American and Hispanic)*	1.44
IRF6rs12205986	interferon-β	**GWAS:** 56 cases, 126 IFN-β exposed controls *(European)*	8.3

GWAS=genome-wide association study; CGS=candidate gene study; T=treated with same drug; P=population; anti-TB drugs=isoniazid, rifampicin, pyrazinamide.

Appendix 6 – References

4 Kaliyaperumal K, Grove JI, Delahay RM, Griffiths WJH, Duckworth A, Aithal GP. Pharmacogenomics of drug-induced liver injury (DILI): Molecular biology to clinical applications. J Hepatol. 2018;69(4):948-57. (Journal full text)

5 Nicoletti P, Aithal GP, Chamberlain TC, Coulthard S, Alshabeeb M, Grove JI, *et al.*, for the International Drug-induced Liver Injury Consortium (iDILIC). Drug-induced injury due to flucloxacillin: relevance of multiple HLA alleles. Clin Pharmacol Ther. 2019;106(1):245–253. (PubMed)

6 Cirulli ET, Nicoletti P, Abramson K, Andrade RJ, Björnsson ES, Chalasani N, *et al;* Drug-Induced Liver Injury Network (DILIN) investigators; International DILI consortium (iDILIC). A Missense Variant in PTPN22 is a Risk Factor for Drug-induced Liver Injury. Gastroenterology. 2019;156(6):1707–1716.e2. (PubMed)

7 Kowalec K, Wright GEB, Drögemöller BI, Aminkeng F, Bhavsar AP, Kingwell E, *et al*. Common variation near IRF6 is associated with IFN-β-induced liver injury in multiple sclerosis. Nat Genet. 2018;50(8):1081-5. (PMC full text)

APPENDIX 7. DILI registries and epidemiological studies

DILI registries

Spanish DILI Registry [8]

The Spanish DILI Registry (http://spanishdili.uma.es) is the pioneer of DILI registries with its initiation dating back to 1994. Various hepatology and pharmacology units from all over Spain participate in this national registry, which is coordinated by the Spanish DILI group at Málaga University. The main objective of this registry is to prospectively identify and record a large number of DILI cases that can be used to enhance the understanding of DILI both from a clinical and biological perspective. Hence, all participating units in the Spanish DILI Registry uses the same structured report form for data collection to ensure that necessary information is recorded for all cases in a standardized manner. In addition to demographic and clinical data, biological samples are also collected for mechanistic studies.

The inclusion criteria for case recruitments [9] were initially the DILI consensus definition determined by a panel of experts in 1989: 1) ALT or CBL >2× ULN or 2) a combined increase in AST, ALP or TBL provided one of them is >2X ULN.[9] However, the registry updated its inclusion criteria in 2011 with the publication of the new consensus criteria, which state that a clinically important DILI case should fulfil one of the following conditions: 1) ALT ≥5 × ULN, 2) ALP ≥2 × ULN or 3) ALT ≥3 × ULN + TBL >2 × ULN.

All potential DILI cases reported to the registry are diagnosed by a panel of experts at the coordinating centre and the CIOMS causality assessment scale is applied to all drug-induced cases for comparative purposes. By the end of 2016 the Spanish DILI Registry had recruited 946 DILI cases, which have been the bases for a number of published epidemiological and mechanistic studies. [*8*, 10, 11, 12, 13, 14, 15]

Drug-Induced Liver Injury Network (DILIN) [16]

The US DILI Registry Network, DILIN (http://dilin.org/), was established in 2003 by the National Institute of Health. The rationale behind this initiation was to improve the understanding of DILI risk factors, natural history and biological basis through prospective DILI case recruitments.[17] DILIN was initially comprised of five clinical sites, but has since grown to include eight clinical sites, of which many have developed local or regional referral networks (satellite sites) to increase the number of case enrolments.

The inclusion criteria adopted by this registry are: 1) age >2 years, 2) enrolment within 6 months from DILI (due to conventional drugs or HDS) onset, 3) fulfil any of the following laboratory criteria: i) ALT or AST >5 × ULN or ALP >2 × ULN on two consecutive occasions; ii) TBL >2.5 mg/dL and elevated AST, ALT or ALP; iii) INR >1.5 and elevated AST, ALT or ALP. In contrast, cases with acetaminophen hepatotoxicity, underlying liver diseases that can confound the diagnosis, or liver or bone marrow transplant prior to enrolment are excluded from the DILIN registry.

Causality assessment is performed through consensus expert opinion, i.e. a panel of three experienced hepatologists independently review available case information in order to determine a DILIN causality score. The score is based on a set of descriptions and percentage likelihoods (definite: >95% likelihood of DILI, highly likely: 75-95%, probable: 50-74%, possible: 25-49%, unlikely <25%) and differs from the CIOMS scale. This causality assessment system was developed by DILIN at its initial stage in an attempt to provide a standardized and more objective approach.[18] In addition to clinical data, DILIN also collect urine and blood samples, which are stored at the NIDDK biosample repository at Rutgers University (Piscataway, NJ, USA) As of 2015, DILIN has recruited 1257 DILI cases and has published various epidemiological and mechanistic studies based on the growing case collection.[16, 19, 20, 21, 22, 23, 24]

Acute Liver Failure Study Group (ALFSG) [25]

Similar to DILIN, ALFSG (http://www.utsouthwestern.edu/labs/acute-liver/) is a clinical research network in the US funded by the National Institutes of Health. It was initiated in 1997 with the aim to prospectively study patients with serious liver condition. Its focus, however, is not limited to drug-induced ALF cases, but embraces all causes of ALF. In 2008 ALFSG expanded its focal point to also include less severe cases, i.e. cases with acute liver injury (ALI).

The eligibility criteria for ALF recruitments include: 1) encephalopathy, 2) coagulopathy (INR ≥1.5), and 3) acute onset of illness <26 weeks, while those for ALI include: 1) acetaminophen (APAP)-induced acute illness <2 weeks, 2) INR ≥2, ALT ≥10 × ULN and non-APAP-induced acute illness <26 weeks or 3) INR ≥2, ALT ≥10 × ULN and TBL ≥3 mg/dL.

There are currently 15 recruitment centres in ALFSG and the coordinating centre is located at the Southwestern Medical Centre (UTSW). ALFSG collects clinical and epidemiological data as well as serum, plasma, urine, tissue and DNA samples of recruited ALF and ALI patients. As of 2016, more than 3000 patients have been enrolled, with biospecimen having been accrued from the majority. A number of publications have resulted from the work of ALFSG, including reports on idiosyncratic drug-induced ALF.[25, 26]

Japanese DILI registry [27]

A national collaboration to prospectively collected DILI cases in Japan was initiated in 2010 and currently comprises 27 hospitals all over Japan. The Japanese DILI registry is managed in cooperation with the Japanese National Institute of Health Sciences, the coordinating centre is located at Teikyo University Hospital.

DILI cases to be included in this registry must fulfil at least one of the following criteria: 1) ALT ≥150 IU/L or 2) ALP ≥2 × ULN. Demographic and clinical information is recorded for each recruited DILI case and blood and urine samples are collected twice from the patient (at the time of DILI detection and after the episode). These samples will be used for DILI biomarker studies, including miRNA screenings. Hence, blood and urine samples are also collected from patients with other liver conditions, such as hepatocellular carcinoma, primary biliary cirrhosis or autoimmune hepatitis, for comparative purposes.

Each DILI case is adjudicated by the individual hepatologist in charge of the patient, who is required to supply a CIOMS score as well as a DDW-J 2004 score for each case to be enrolled in the registry. The DDW-J scale is a modified version of the CIOMS scale, which takes into consideration drug lymphocyte stimulation test and eosinophilia (≥6%), while disregarding comedication and age; previous information on hepatotoxicity of the drug is scored either 0 or 1.[28]

Findings from 307 DILI cases collected prospectively between 2010 and 2018 have been published.[27] Of these, 64% were hepatocellular, 20% were mixed type and 16% cholestatic, representing a shift from cholestatic to hepatocellular injury possibly due to decreased prescription of drugs with a potential to cause cholestatic DILI such as tiopronin and ticlopidine [29, 30]. Fifty-three percent of DILI cases occurred within 30 days and 79% of DILI cases occurred within 90 days after starting drug administration. Using the DDW-J scale [28] 93.8% of cases were diagnosed as "highly probable", and 5.9% as “possible”, suggesting the usefulness of this scale. The top five categories of causal drugs were anti-inflammatory drugs (11%), anti-microbial drugs (11%), anti-cancer drugs (10%), dietary supplements (9%), and drugs for the gastrointestinal system (9%). The percentage of anti-microbial drugs was lower than that in North America

and Europe, possibly because doctors in Japan are well aware of anti-microbial DILI and are not are not necessarily referring these cases to hepatologists. Drug lymphocyte stimulation testing (DLST) was performed in 59% of cases and was positive in 48%. Eosinophilia $\geq 6\%$ was observed in 27% of cases, which was similar to previous findings from an earlier survey of retrospectively collected DILI cases [31].

Dietary supplement-induced DILI had a longer time to onset than medicines, with only 48% of cases occurring within 90 days. A long time to onset of DILI in Japan has been reported before for dietary supplements [32] and for Chinese herbal medicines [*31*]; the reason is unknown. Chinese herbal medicines are widely used in Japan, and more than 100 such products have been approved by the Ministry of Health, Labour and Welfare (MHLW). Therefore, DILI cases due to dietary supplements and Chinese herbal medicines are collected separately in Japan.

Cases of liver injury are reported spontaneously to the Pharmaceuticals and Medical Devices Agency (PMDA) by doctors all over Japan. In reports between 2007 and 2016 the most frequently reported causal drugs were terbinafine (369 cases), carbamazepine (284 cases), clopidogrel (276 cases), loxoprofen (250 cases), gefitinib (236 cases), tegafur-uracil (209 cases), isoniazid (204 cases), ticlopidine (204 cases), allopurinol (171 cases) and atorvastatin (171 cases).

Latin American DILI Network (LATINDILI) [33]

The LATINDILI registry is a multinational DILI registry created in 2011 through an initiative from the Spanish DILI group, which is supporting this new registry in terms of coordination and database management. Existing differences in drug prescription patterns and self-medications in Latin America compared to Europe and North American and the fact that collaborative efforts in DILI research were virtually non-existent in Latin America prior to 2011, prompted the Spanish DILI group to approach Latin American hepatologists with the idea of establishing a multinational DILI Registry. At present, hepatology units from ten different countries (Argentina, Brazil, Chile, Ecuador, Mexico, Peru, Paraguay, Uruguay and Venezuela) collaborate in LATINDILI.

Being coordinated by the Spanish DILI group, LATINDILI has the same operational structure as the Spanish DILI Registry in terms of inclusion criteria, data collection and causality assessment.

All cases reported to LATINDILI are assessed for causality through expert opinion by a panel of experienced hepatologists in Málaga. To date, 280 DILI cases have been recruited in LATINDILI. A preliminary study on the first 200 DILI cases has been performed and a publication on the epidemiological findings from the first 300 DILI cases in LATINDILI have been released [34].

Prospective European DILI Registry (Pro-Euro-DILI Net) [35]

The Pro-Euro-DILI Registry is a relatively new multinational European DILI registry. It was initiated in 2014 through the successful application for an EASL registry research grant. This registry is jointly coordinated from the Málaga University (Spain) and the Nottingham University (UK) and currently has collaborating hospital units in Switzerland, Germany, France, Iceland, Italy and Portugal. It is anticipated that national networks of collaborating hospital centres led by a designated country coordinator will be established in each country. The aim of the Pro-Euro-DILI Registry is to prospectively enrol idiosyncratic DILI cases with in-depth phenotype data. In addition, well characterised control cases, patients exposed to the same causative agents without developing DILI, are also enrolled for comparative purposes in mechanistic/biomarker studies.

The Prospective European DILI Registry includes DILI cases >18 years of age and with ALT ≥5 × ULN, ALP ≥2 × ULN or ALT ≥3 × ULN + TBL >2 × ULN.

All cases are diagnosed primarily by local hepatologists and are thereafter assessed by an adjudication committee consisting of DILI experts from various countries. Cases adjudicated as non-DILI due to the presence of plausible alternative causes are classified as acute liver injury unrelated to drugs and stored as a potential control group for future studies. Serial biosamples (blood and urine) are collected from the time of DILI detection throughout the episode until liver profile normalization. Due to the recent initiation of this registry the number of recruited DILI cases (111 as of June 2019) is still too low to perform epidemiological or mechanistic studies.

The Indian Network of DILI (INDILI network)

Led and coordinated by Harshad Devarbhavi, this initiative was set up back in 2013 and the nodal point of all case collection is St. John's medical college Hospital, Bangalore. This endeavour was undertaken under the aegis of Indian Association for study of liver disease (INASL) the national association for liver disease. The network is spread thorough the country, including 20 centres and a few gastroenterologists contributing cases (in 4 years). It does not have paracetamol cases, which is not common in India.

The network enrols patients with DILI based on International Expert Group recommendations [9] and uses RUCAM for case adjudication. It has assembled over 1250 cases, of which 46% were related to anti-tuberculosis medicines and 13% to complementary and alternative medicines. No biological samples are collected. The network collects whole blood (for DNA) and serum at the time of initial visit/ diagnosis. There are no serial samples available.

The network plans to analyze the results and submit it to the AASLD and simultaneously write about it. Preliminary data was presented at the July 2017 annual meeting of INASL.

The Indian Antituberculous (ATB) DILI study

This study is led by GP Aithal. So far, two centres (Christian Medical College, Vellore, Tamil Nadu and St John's Medical College, Bengaluru, Karnataka have enrolled patients for the ATB-studies); 117 ATB-DILI cases and 220 controls (drug-exposed controls and healthy controls) have been recruited. Half the cases were excluded due to low quality DNA extracted, but the clinical and phenotypic data is quite credible.

DILI registry in China

The DILI registry of China is core of the platform of Hepatox (www.hepatox.org), which went online in July 2014. The main purposes and functions of Hepatox are: 1) facilitating collaborative research programs; 2) registering nationwide DILI patients; 3) providing tools for DILI researchers and clinicians; 4) promoting DILI awareness to public; 5) providing drug and HDS information which has been reported to cause DILI.

The DILI registry of China started with a retrospective study which included a total of 25 927 confirmed DILI cases hospitalized from 2012 through 2014 at 308 medical centers in mainland China, collecting demographic, medical history, treatment, laboratory, disease severity, and mortality data from all patients [36]. Investigators at each site were asked to complete causality assessments for each case according to the Roussel Uclaf Causality Assessment Method (RUCAM). Cases with RUCAM scores less than 6 were reviewed by a panel of 3 hepatologists with DILI expertise (consistent with the expert opinion method of causality assessment). Most cases of DILI presented with hepatocellular injury (51%), followed by mixed injury (28%) and cholestatic injury (20%). The leading single classes of implicated drugs were traditional

Chinese medicines or herbal and dietary supplements (27%) and anti-tuberculosis medications (22%). Chronic DILI occurred in 13% of the cases and, although 44% of the hepatocellular DILI cases fulfilled Hy's Law criteria, only 280 cases (1.08%) progressed to hepatic failure, 2 cases underwent liver transplantation (0.01%), and 102 patients died (0.39%). Among the 102 deaths, DILI was judged to have a primary role in 72 cases, a contributory role in 21 cases and no role in 9 cases. Assuming that the proportion of DILI in the entire hospitalized population of China was represented by that observed in the 66 centres where DILI capture was complete, the annual incidence in the general population was estimated to be 23.8 per 100,000 persons. Traditional Chinese medicines, herbal and dietary supplements, and anti-tuberculosis drugs were the leading causes of DILI in mainland China.

After the retrospective study, the registry based on Hepatox enrolled another 6663 DILI cases prospectively (named DILI-P research) as of April 2019 and the data are being analyzed. Thus, there are more than 30 000 retrospective and prospective DILI cases in the Hepatox database. The DILI-P research will keep ongoing for a long time.

For liver injury induced by traditional medicines and herbal and dietary supplements (HDS), specific clinical guidelines and governmental regulatory guidance have been released in China [37, 38]. A retrospective cohort study and case-control study have been carried out to systematically analyze the clinical characteristics of Chinese herbal medicine-related liver injury and the frequently implicated herbal agents [39, 40]. Among them, *Polygonum multiflorum*, *Psoralea corylifolia* and *Epimedium brevicornu* contributed as major causes, and these herbs have been proven to cause immune stress-mediated idiosyncratic DILI [41, 42, 43, 44]. A prospective cohort study found that the HLA-B*35:01 allele is a potential biomarker for prediction of liver injury risk of *Polygonum multiflorum* [41]. Based on the relevant studies, comprehensive measures were instituted by the regulatory authority of China to prevent and manage the risks associated with herbal medicines.

To promote the risk control of HDS-induced DILI, experts from China, France, Spain, Iceland and the United States set up a Consortium for the Safety Study of Traditional Medicines (CSSTM) in 2018 and released the “Beijing Declaration on the Safe Use of Traditional Medicines [45]. With support from the Consortium, Chinese scholars have built an internet platform for drug safety information inquiries. The current version 1.0 provides information on liver associated with drugs, including traditional Chinese medicines, herbal and dietary supplements. The system is based on Chinese national regulatory data with currently more than 6.5 million adverse event reports, and is monitored in real-time at national level. An English version is intended to be launched. The medicines regulatory authority of China has also launched an electronic medical records-based ADR surveillance system to collect data on DILI and other kinds of drug-induced diseases.

Epidemiological studies based on large DILI cohorts

Reports on large DILI cohorts can be found in the literature, in which DILI cases have been collected for the purpose of epidemiological studies (**Table 3-1**). These studies vary considerably with regard to clinical setting and design. Some identify DILI cases prospectively, while others rely on retrospective identification through hospital records. The studies can involve single hospital units or multiple hospital collaborations and may focus on liver injury induced by a specific causative agent by drugs and/or herbal and dietary supplements (HDS) in general. The definition of HDS products as potential causative DILI agents is a particularly difficult area with regard to harmonizing the classifications.[46]

More importantly, the definition of DILI also varies considerably between studies, making it difficult to compare the findings. The use of clinical chemistry criteria that are less stringent than those accepted in 2011 [2] may lead to the inclusion of cases that do not necessarily represent clinically important liver injury, and could lead to an overestimation of DILI frequency. In addition, retrospectively identified cases may not always include complete case data, which could jeopardize a reliable causality assessment. DILI definitions and nomenclature need to be standardized in order to obtain more informative results from independent DILI cohorts. Attempts to address this problem have been made through organization of international clinical research workshops attended by representatives from currently existing DILI registries.[47]

Table 3-1. Large DILI cohorts collected for epidemiological studies

	Iceland [48]	**China** [36]	**Korea** [46]	**Turkey** [49]	**India** [50]	**Japan** [31]
Participating hospital units	Multiple hospitals	Multiple hospitals	Multiple hospitals	Single hospital	Single hospital	Multiple hospitals
Time period	2010-2012 (2 years)	2012-2014 (3 years)	2005-2007 (2 years)	2001-2007 (6.5 years)	1997-2008 (12 years)	1997-2006 (10 years)
Data collection	Prospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective
Inclusion criteria	>15 years, ALT >3 × ULN; or ALP >2 × ULN	Hospitalized patients,dis-charge diagnoses indicated a DILI event confirmed by RUCAM or expert opinion, liver chemist-ries abnormal	Hospitalized adults, ALT >3 × ULN or TBL >2 × ULN	>15 years; Alcohol/day <15 g (women) and 20 g (men), CIOMS consensus criteria*	TBL >2mg/dL; AST or ALT >3 × ULN; or ALP >2 × ULN	ND
Exclusion criteria	Acetamino-phen (para-cetamol) toxicity			HDS toxicity		
Causality assessment tool	RUCAM scale	RUCAM scale or expert opinion	RUCAM scale	ND	RUCAM scale	DDW-J 2004 score
Number of DILI cases	96	25927	371	170	313	1676
Patient sex, M | F **(%)**	44 | 56	50.83 | 49.17	37 | 63	44 | 56	58 | 42	43 | 57
Mean#/medianβ age (range) at DILI onset	55β (16-91)	46# (1-90)	49β (16-79)	43# (15-77)	39# (12-84)	55# (12-99)
Causative agents (%) Drugs | HDS	84 | 16	73.19 | 26.81	27 | 63	100 | –	98.7 | 1.3	83 | 17

*CIOMS consensus criteria: 1) ALT or CBL >2 × ULN or 2) a combined increase in AST, ALP or TBL provided one of them is >2 × ULN (see reference [51]).

ALT=alanine aminotransferase, ALP=alkaline phosphatase, AST=aspartate aminotransferase, CBL=conjugated bilirubin, HDS=herbal and dietary supplements, INR=international normalized ratio, ND=no data, TBL=total bilirubin, ULN=upper limit of normal

Appendix 7 – References

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APPENDIX 8. Information on DILI risks shown in product information of selected drug classes

Anti-cancer drugs

Appendix 8, Table 1. Communication on hepatotoxicity in the U.S. product labels of 40 oncology products

This table illustrates the point that, unlike products in other therapeutic areas, many anti-cancer therapies stay on the market despite their hepatotoxic potential.

Notes: (1) The table may not include every new therapeutic class of oncologic treatments and only lists some products as examples. (2) Risk data can evolve with new patient populations, combined treatments and other factors. Sources such as updated product labels, regulatory agency websites and the LiverTox® database should be consulted if detailed information for a product is required.

Class	Drug	Detected pre-marketing	Monitoring recommen-dations	Boxed warning	REMS	Fatal cases
Chemotherapy drugs	belinostat [52]	**Yes**	**Yes**	No	No	**Yes**
	calaspargase pegol [53]	**Yes**	**Yes**	No	No	n/s
	cisplatin [54]	No	**Yes**	No	n/a	n/s
	docetaxel [55]	**Yes**	**Yes**	**Yes**	No	**Yes**
	doxorubicin [56]	**Yes**	**Yes**	No	n/a	n/s
	fluorouracil (5-FU) [57]	No	No	No	n/a	n/s
	irinotecan [58]	No	No	No	n/a	n/s
Hormonal agent	abiraterone [59]	**Yes**	**Yes**	No	No	**Yes**
Kinase inhibitors	alpelisib [60]	**Yes****	No	No	No	n/s
	axitinib [61]	**Yes**	**Yes**	No	No	n/s
	copanlisib [62]	**Yes****	No	No	No	n/s
	crizotinib [63]	**Yes**	**Yes**	No	No	**Yes**
	duvelisib [64]	**Yes**	**Yes**	No	No	n/s
	entrectinib [65]	**Yes**	**Yes**	No	No	n/s
	erdafitinib [66]	**Yes****	No	No	No	n/s
	ibrutinib [67]	**Yes**	**Yes**	No	No	n/s
	idelalisib [68]	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
	imatinib [69]	**Yes**	**Yes**	No	n/a	**Yes**
	lapatinib [70]	**Yes**	**Yes**	**Yes**	No	*
	larotrectinib [71]	**Yes**	**Yes**	No	No	n/s
	pazopanib [72]	**Yes**	**Yes**	**Yes**	No	**Yes**
	pexidartinib [73]	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
	ponatinib [74]	**Yes**	**Yes**	**Yes**	No	**Yes**
	regorafenib [75]	**Yes**	**Yes**	**Yes**	No	**Yes**
	sunitinib [76]	**Yes**	**Yes**	**Yes**	No	**Yes**
	zanubrutinib [77]	**Yes**	**Yes**	No	No	n/s
EGFR inhibitors	cetuximab [78]	No	No	No	n/a	n/s
	erlotinib [79]	**Yes**	**Yes**	No	n/a	**Yes**
	gefitinib [80]	**Yes**	**Yes**	No	n/a	n/s
Checkpoint inhibitors	atezolizumab [81]	**Yes**	**Yes**	No	No	**Yes**
	avelumab [82]	**Yes**	**Yes**	No	No	n/s
	nivolumab [83]	**Yes**	**Yes**	No	No	n/s
	pembrolizumab [84]	**Yes**	**Yes**	No	No	n/s
	ipilimumab [85]	**Yes**	**Yes**	**Yes**	No	**Yes**
Anti-drug conjugates	brentuximab vedotin [86]	**Yes**	**Yes**	No	No	**Yes**
	gemtuzumab ozogamicin [87]	**Yes**	**Yes**	**Yes**	n/a	**Yes**
	inotuzumab ozogamicin [88]	**Yes**	**Yes**	**Yes**	No	**Yes**
	ado-trastuzumab emtansine [89]	**Yes**	**Yes**	**Yes**	No	**Yes**
	fam-trastuzumab deruxtecan-nxki [90]	**Yes****	No	No	No	**Yes**
	polatuzumab vedotin-piiq [91]	**Yes**	**Yes**	No	No	n/s
Total "Yes"		36 of 40	33 of 40	12 of 40	2 of 30	19 of 40

Legend:

Detected pre-marketing	Hepatotoxicity discovered before marketing authorization was granted
Monitoring guidance	Guidance for monitoring included on the label
Boxed warning	Boxed warning for DILI
REMS	Risk evaluation and mitigation strategy (REMS) required (for products approved in the U.S. after 2007)
Fatal cases	Fatal liver injury cases reported

n/a	Not applicable
n/s	Not specified in product information
*	Causality of deaths uncertain
**	Mild elevation of ALT/AST

Tuberculosis chemotherapies

Appendix 8, Table 2. Guidance for monitoring and warnings included in the prescribing information of selected anti-TB drugs

Notes: (1) The information in the above table is not complete or comprehensive as the product information approved by different regulatory authorities may not be identical. In addition, not all of the drugs shown are approved for treatment of tuberculosis in all countries, although they may be licensed for other indications. (2) Risk data can evolve with a variety of factors. Sources such as updated product labels, regulatory agency websites and the LiverTox® database should be consulted if detailed information for a product is required.

WHO classification • Drug	Caution in pre-existing liver disease	Warning	Boxed warning	Monitoring recommenda-tions	Fatal cases
Group 1: 1st line treatment					
• Isoniazid U [92]	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
• Rifampicin U [93]	**Yes**	**Yes**	No	**Yes**	**Yes**
• Ethambutol U [94]	**Yes**	**Yes**	No	**Yes**	**Yes**
• Pyrazinamide U[95]	**Yes**	**Yes**	No	**Yes**	No
Group 2: Parenteral agents					
• Streptomycin U[96]	No	No	No	No	No
• Kanamycin U [97]	No	No	No	No	No
• AmikacinU [98]	No	No	No	No	No
• Capreomycin U [99]	No	**Yes**	No	**Yes**	No
Group 3: Fluoroquinolones					
• Levofloxacin U [100]	No	**Yes**	No	No	**Yes**
• Moxifloxacin U [101]	**Yes**	**Yes**	No	No	No
• Gatifloxacin U [102]	No	No	No	No	No
• Ofloxacin U [103]	No	**Yes**	No	**Yes**	No
Group 4: Oral 2nd –line drugs					
• Ethionamide U [104]	**Yes**	**Yes**	No	**Yes**	No
• Cycloserine U [105]	**Yes**	**Yes**	No	**Yes**	No
• *p*-Aminosalicylic acid U [106]	**Yes**	**Yes**	No	**Yes**	No
Group 5: Treatment of MDR (limited data on efficacy and/or long-term safety, includes new anti-TB agents)					
• Linezolid U [107]	No	**Yes**	No	No	No
• Clofazimine U [108]	No	**Yes**	No	No	No
• AmoxicillinE [109]	No	**Yes**	n/a	**Yes**	No
• Imipenem/cilastatin U [110]	No	**Yes**	No	**Yes**	No
• MeropenemU [111]	No	**Yes**	No	No	No
• High-dose isoniazid	(see Group 1 above)				
• Delamanid E [112]	**Yes**	Yes	n/a	No	No
• Bedaquiline U [113]	No	Yes	No	**Yes**	No
• Clarithromycin U [114]	No	Yes	No	No	**Yes**
Total "Yes" (of 23 medicines)	9	19	1	12	5

Legend:
Prescribing information reviewed: **U**=U.S. FDA, **E**=U.K Medical and Health products Regulatory Agency.

Caution in pre-existing liver disease	Warning/contraindication/caution on use in patients with liver dysfunction
Warnings	Hepatotoxicity/abnormalities caused by drug mentioned in Warnings, precautions and adverse events section of product label
Boxed warning	Boxed warning for DILI (applies to U.S. FDA-approved product information only)
Monitoring recommendations	Recommendations for monitoring of liver function
Fatal cases	Fatal DILI cases mentioned in product information

Antiretrovirals

Appendix 8, Table 3. Information on DILI risks published in U.S. FDA-approved labels of selected antiretrovirals

Notes: (1) Where possible the U.S. FDA-approved prescribing information was used. The information in the table is not complete or comprehensive as the prescribing information approved by other regulatory authorities may not be identical. (2) Risk data can evolve with a variety of factors. Sources such as updated product labels, regulatory agency websites and the LiverTox® database should be consulted if detailed information for a product is required.

Antiretroviral class Example	Caution in pre-existing liver disease	Warnings	Boxed warning	Monitoring recommen-dations	Fatal cases
Nucleoside reverse transcriptase Inhibitor (NRTI) Example: Lamivudine [115]	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Non-nucleoside reverse transcriptase inhibitor (NNRTI) Example: Efavirenz [116]	**Yes**	**Yes**	No	**Yes**	**Yes**
Integrase strand transfer inhibitors (INSTI)					
Example 1: Raltegravir [117]	No	No**	No	No	**Yes****
Example 2: Dolutegravir [118]	**Yes**	**Yes**	No	**Yes**	No
Protease Inhibitor (PI) Example: Ritonavir [119]	**Yes**	**Yes**	No	**Yes**	**Yes**
Uptake (CXCR5) inhibitor Example: Maraviroc [120]	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Fusion Inhibitor Example: Enfuvirtide [121]	No	No	No	No	No
Total "Yes" (of 7 example medicines)	5	5	2	5	5

Legend:

* Information from U.S. FDA-approved package inserts

** Cases have been associated with immune reconstitution inflammatory syndrome (IRIS)

Caution in pre-existing liver disease	Warning/contraindication/caution on use in patients with liver dysfunction
Warnings	Hepatotoxicity/abnormalities caused by drug in Warnings, precautions and adverse events in Prescribing Information
Boxed warning	Boxed warning for DILI
Monitoring recommendations	Recommendations for monitoring of liver function
Fatal cases	Fatal DILI cases have been reported

Appendix 8 - References

52 Prescribing information for Beleodaq®. Revised 4/2017. (PDF)
53 Prescribing information for Asparlas®. Revised 12/2018. (PDF)
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58 Prescribing information for Camptosar®. Revised 2/2019. (PDF)
59 Prescribing information for Zytiga®. Revised 6/2019. (PDF)
60 Prescribing information for Piqray®. Revised 5/2020. (PDF)
61 Prescribing information for Inlyta®. Revised 1/2020. (PDF)
62 Prescribing information for Aliqopa®. Revised 2/2020. (PDF)
63 Prescribing information for Xalkori®. Revised 6/2019. (PDF)
64 Prescribing information for Copiktra®. Revised 9/2018. (PDF)
65 Prescribing information for Rozlytrek®. Revised 8/2019. (PDF)
66 Prescribing information for Balversa®. Revised 4/2019. (PDF)
67 Prescribing information for Imbruvica®. Revised 11/2019. (PDF)
68 Prescribing information for Zydelig®. Revised 7/2014. (PDF)
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71 Prescribing information for Vitrakvi® . Revised 11/2018. (PDF)
72 Prescribing information for Votrient® . Revised 5/2017. (PDF)
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117 Prescribing information for Isentress®. Revised August 2013. (PDF)
118 Prescribing information for Tivicay®. Revised August 2013. (PDF)
119 Prescribing information for Norvir®. Revised June 2017. (PDF)
120 Prescribing information for Selzentry®. Revised August 2017. (PDF)
121 Prescribing information for Fuzeon®. Issued March 2003. (PDF)

APPENDIX 9. Differences in label safety information on hepatotoxicity: Two examples

Rituximab

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC). It is approved for the following non-oncological indications: rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis.

Table 5-1 shows differences between the EU Summary of Product Characteristics (as of February 2020) and the U.S. product label (as of March 2020) regarding information on hepatic adverse effects (**shaded grey**).

Appendix 9, Table 1. Differences in descriptions risks of hepatic adverse effects for rituximab (non-oncological indications)

EU SmPC	US PI
Contraindications	
Active, severe infections	**None**
Warnings and Precautions	
Cases of hepatitis B reactivation have been reported in subjects receiving rituximab including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. **Limited information from one study in relapsed/refractory CLL patients suggests that rituximab treatment may also worsen the outcome of primary hepatitis B infections.** Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with rituximab. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. **Patients with active hepatitis B disease should not be treated with rituximab.** Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.	Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, **hepatic failure** and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab. **Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).** HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur. Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with rituximab. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during rituximab treatment. **Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following rituximab therapy. HBV reactivation has been reported up to 24 months following completion of ritxuimab therapy.** **In patients who develop reactivation of HBV while on**

EU SmPC	US PI
	rituximab, immediately discontinue rituximab and any concomitant chemotherapy, and institute appropriate treatment. **Insufficient data exist regarding the safety of resuming rituximab in patients who develop HBV reactivation. Resumption of rituximab in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B.**
Undesirable effects	
None pertaining to hepatic disorders other than reactivation of HBV	None pertaining to hepatic disorders other than reactivation of HBV
Pharmacokinetics	
No pharmacokinetic data are available in patients with hepatic or renal impairment. and no change in dosing recommended	No formal studies were conducted to examine the effects of hepatic impairment on the pharmacokinetics of rituximab. and no change in dosing recommended

Information provided for rituximab in LiverTox® [122]is generally consistent with that provided in the EU SmPC and US label. However, additional information not shown in the product label includes details on serum aminotransferase elevations. These laboratory abnormalities are listed as an adverse reaction in neither the EU SmPC nor the U.S. label except in the context of HBV reactivation, since they are not more common than with therapy without rituximab (i.e. there appears to be no additive effect). In addition, more detailed information on the risk of hepatitis B reactivation is provided in LiverTox® than the product labels, however not impacting the most appropriate management of the risk. It should be noted that, in line with regulatory guidelines, the product label is not intended to give general advice on medical conditions or on monitoring procedures that are well established clinical practice.

Finally, details on the postulated mechanism of injury are provided in LiverTox®. The mechanism of liver injury in reactivation of hepatitis B appears to be a brisk immunological response to rising levels of viral antigens on hepatocytes. Injury often arises after rituximab therapy has stopped or between courses of treatment.

Natalizumab

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4-subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. It is indicated as single disease-modifying therapy in adults with highly active relapsing remitting multiple sclerosis (in the U.S. also for Crohn's Disease).

Table 5-2 shows differences between the EU Summary of Product Characteristics (as of November 2019)) and the U.S. label (as of August 2019) regarding information on hepatic adverse effects (**shaded grey**).

Appendix 9, Table 2. Differences in label safety information on risks of hepatic adverse effects of natalizumab

EU SmPC	US PI
Contraindications	
None pertaining to hepatic disorders	None pertaining to hepatic disorders
Warnings and Precautions	
Spontaneous serious adverse reactions of liver injury have been reported during the post marketing phase. These liver injuries may occur at any time during treatment, even after the first dose. In some instances, the reaction reoccurred when natalizumab was reintroduced. Some patients with a past medical history of an abnormal liver test have experienced an exacerbation of abnormal liver test while on natalizumab. **Patients should be monitored as appropriate for impaired liver function, and be instructed to contact their physician in case signs and symptoms suggestive of liver injury occur, such as jaundice and vomiting.** In cases of significant liver injury natalizumab should be discontinued.	Clinically significant liver injury has been reported in patients treated with natalizumab in the postmarketing setting. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose; signs of liver injury have also been reported for the first time after multiple doses**. In some patients, liver injury recurred upon rechallenge, providing evidence that natalizumab caused the injury.** The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. Natalizumab should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence).
Undesirable effects	
Spontaneous cases of serious liver injuries, increased liver enzymes, hyperbilirubinaemia have been reported during the post marketing phase. **No data from clinical trials disclosed.**	Abnormal liver function test **(5% vs. 4% in placebo controls in clinical trials).**
Pharmacokinetics	
The pharmacokinetics of natalizumab in patients with renal or hepatic insufficiency has not been studied. The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in patients with renal or hepatic impairment.	Pharmacokinetics of natalizumab in patients with renal or hepatic insufficiency have not been studied. and no change in dosing recommended

Information provided for this product in LiverTox® [123] is generally consistent with that provided in the EU SmPC and US PI. However, additional information is provided on the incidence of abnormal liver tests in clinical trials [124, 125] as well as on six instances of hepatic injury reported to the U.S. FDA's Adverse Event Reporting System (FAERS) [126]. These six cases were all associated with jaundice. The onset of injury followed the initial infusion of natalizumab in four patients, and after 5 and 12 courses of treatment in the other two reported cases. The pattern of liver injury was hepatocellular in five cases and cholestatic in one. Several cases were accompanied by autoantibodies and were treated with corticosteroids, but autoimmune features were not prominent and immunoallergic features (fever, rash, eosinophilia) were not

reported. The clinical cases were moderate in severity, and no patient developed acute liver failure or progressed to chronic liver injury or vanishing bile duct syndrome.

Natalizumab can cause immune suppression and has been linked to bacterial and viral infections, but interestingly has not been reported to cause reactivation of tuberculosis or hepatitis B. Nevertheless, because of its mechanism of action, it should be considered as a potential cause of reactivation.

Finally, details on the postulated mechanism of injury are provided. The mechanism of liver injury caused by natalizumab is probably immunologically mediated, perhaps as a result of its effects on leukocyte function. It is a monoclonal antibody and like other proteins it is taken up by cells by endocytosis and is metabolized into amino acids.

Appendix 9 – References

122 LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-2020. Rituximab. Updated 18 June 2018. (**Webpage**)

123 LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-2020. Natalizumab. Updated 18 June 2015]. (**Webpage**)

124 Keeley KA, Rivey MP, Allington DR. Natalizumab for the treatment of multiple sclerosis and Crohn's disease. Ann Pharmacother 2005; 39: 1833-43. (**PubMed**)

125 Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, *et al*.; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354: 899-910. [**Free full text**]

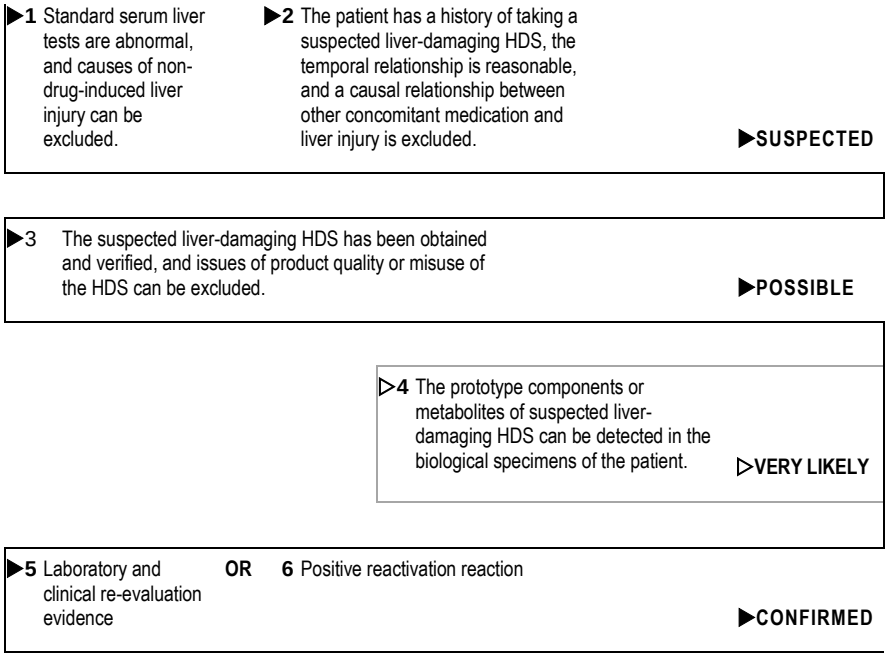
126 Bezabeh S, Flowers CM, Kortepeter C, Avigan M. Clinically significant liver injury in patients treated with natalizumab. Aliment Pharmacol Ther. 2010;31(9):1028–1035. doi:10.1111/j.1365-2036.2010.04262.x. (**Free full text**)

APPENDIX 10. Example of a causality assessment process for HDS-induced liver injury: the algorithm used in China

Adapted from: [127]

HDS-induced liver injury can be excluded if the causality of liver injury can be attributed to clear non-drug causes, the relationship between the occurrence of liver injury and the time of taking the evaluated HDS is not reasonable, and the causal relationship of liver injury with drugs can be attributed to drugs other than the evaluated HDS.

Otherwise, causality is evaluated by considering Points 1–6 as shown in the flowchart below, as follows: *Suspected*: Points 1 + 2; *Possible*: *Suspected* + Point 3; *Very likely*: *Possible* + Point 4; *Confirmed*: *Possible* + Point 5 or 6, or *Very likely* + Point 5 or 6.



Notes on Points 1 to 6:

1 The determination of the abnormality of liver biochemical indicators is based on the biochemical indicators of DILI, that is, when any one of the following three situations occurs:
(1) ALT ≥ 5 × ULN;
(2) ALP ≥ 2 × ULN, especially when this result is accompanied by an increase in 5'-nucleotidase or GGT, and an increase in ALP caused by bone disease is excluded; or
(3) ALT ≥ 3 × ULN and TBL ≥ 2 × ULN.

2 If a patient has a history of taking suspected liver-damaging HDS and the temporal relationship is reasonable, the causal relationship between other concomitant or sequential medications and liver injury should be assessed simultaneously. Note that patients sometimes do not report all medications to doctors or researchers, especially nonprescription drugs, Chinese herbal medicines, empirical prescriptions, folk prescriptions and healthcare products. Therefore, the patient should be carefully questioned. The medication history from at least 6 months before the onset of liver injury should be investigated. For concomitant medication, not only the types of drugs and the usage and dosage should be considered but also the start and end dates as well as the existence of a reasonable temporal relationship with liver injury.

3 The suspected or confirmed liver-damaging HDS product should be obtained and its related data verified by a quality assessment, which includes verification of the product's origin, its compliance with specifications (or statements on the label), and whether the HDS product is counterfeit and/or contaminated by harmful foreign substances or illegal chemical additives.

4 Biological specimens can originate for example from serum, urine, liver tissue or hair.

5 Laboratory re-evaluation evidence can be obtained using a variety of toxicology and histology methods, including HDS safety evaluation models and methods associated with clinical syndromes. Clinical re-evaluation evidence can be obtained from both prospective and retrospective clinical studies, combined with clinical biological specimen analysis.

6 A positive drug reactivation reaction is a reliable basis for the ascertainment of DILI causality; however, a negative reactivation reaction cannot be used as evidence to exclude DILI

Appendix 10 – Reference.

127 Wang JB, Zhang L, Guo YM, Bai ZF, Xiao XH. Causality assessment strategies and methods for Chinese medicines-induced liver injury. Acta Pharm Sin 2018;53:920–8. DOI: 10.16438/j.0513-4870.2018-0439 (ResearchGate)

APPENDIX 11. Post-publication updates

This space is reserved for any post-publication updates to the consensus report of the CIOMS Working Group on Drug-Induced Liver Injury. The report is freely available at:
https://cioms.ch/publications/product/drug-induced-liver-injury/