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DRUG-INDUCED LIVER INJURY (P HAYASHI, SECTION EDITOR)

Regional and Racial Differences in Drug-Induced Liver Injury

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Abstract

Purpose of Review To summarize the growing epidemiologic and genetic data that suggest racial and regional differences in drug-induced liver injury (DILI).

Recent Findings Several registries and population-based studies report incidence data across continents from 2 to 24 per 100,000 with China reporting the highest incidence estimate. The agents causing DILI vary by race and region as well. Hepatotoxicity from herbal and dietary supplement is on the rise globally with China reporting the highest levels. Genome-wide association studies are beginning to shed light on racial genetic and HLA variants which may determine the risk of DILI.

Summary DILI risk and outcome vary by race and region due to a combination of epidemiologic and genetic factors. The rise and maturation of DILI registries worldwide are beginning to allow important discoveries in how we should consider the diagnosis of DILI by region and race.

Keywords Hepatotoxicity · Race · Ethnicity · Medications · Herbals · Dietary supplements

Introduction

The role of race in drug-induced liver injury (DILI) spans a wider spectrum than just genetic predisposition. While genetics will undoubtedly clarify the role of race, many other factors go into what brings a patient of a specific race, to take a particular agent, for a particular indication and whether a DILI will occur. From this broader perspective, the factors that influence the relationship between race and DILI span both epidemiology (regional and cultural factors) and genetics. The regional and cultural factors will determine exposure. These factors include prescribing practices, availability and acceptance of herbal agents versus allopathic medications, and prevalent medical disorders requiring treatment in that region. Medicines and herbals used by Han Chinese in China will be far different from those used by Caucasians in Iceland. While still controversial, there are data to suggest that pre-existing chronic liver diseases can influence the risk and course of DILI. The prevalences of viral hepatitis and non-alcoholic fatty liver disease (NAFLD) vary by regions and race.

As for genetics, recent data have identified genetic variants associated with risk of DILI and these variants differ by races. How and when these types of genome-wide sequencing discoveries will translate into clinical practice remains to be seen. However, genetic risk factors for a particular race and region could provide the most cost-effective means of lowering the risk of DILI by changing prescribing practices or targeting certain groups for pre-prescription testing.

This review will highlight landmark and new studies that inform us about race and regional differences in DILI. As trans-continental migration increases, the clinician seeing a more racially diverse patient population will find useful information on the epidemiology of DILI from across the globe. For the researcher, the review will hopefully stimulate new and hone ongoing studies examining race and DILI.

This article is part of the Topical Collection on *Drug-Induced Liver Injury*

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Epidemiology by DILI by Race and Region

Incidence

Over the last 20 years, several DILI registries were initiated and have reported their findings. They now span the globe from China [1••], Japan [2], India [3], USA [4, 5], Iceland

Table 1 Population-based studies reporting incidence of drug-induced liver injury

Location	Sweden [9]	Spain [8]	France [7]	Iceland [6]	China [1]	USA (Delaware) [5]
Incidence per 100 K	2.4	3.4	13.9	19.1	23.8	2.7
Year(s)	1970–2004	1994–2004	1997–2000	2010–2012	2012–2014	2014
Number of cases	784	461	34	96	25,927	23
Race or ethnicity	85% Native Swedish^^	90% Native Spanish~	82% Native French*	93% Native Icelandic^	97% Native Han Chinese	70% Caucasian 22% Black/AA 8% Other
Entry criteria	3× ULN ALT and/ or 2× ULN AP	2× ULN ALT and/ or 2× ULN AP	2× ULN ALT and/ or 2× ULN AP	3× ULN ALT and/ or 2× ULN AP	Discharge diagnoses (no ALT or AP criteria)	5× ULN ALT and/ or 2× ULN AP
Enrollment	Inpatient	Inpatient Outpatient	Inpatient Outpatient	Inpatient Outpatient	Inpatient	Inpatient Outpatient
Top 3 classes	Antibiotics NSAIA Analgesics	Antibiotics [4, 8] Nervous system Musculoskeletal	Antibiotics Psychotropic Hypolipidemics	Antibiotics IM NSAIA	HDS Anti-Tuberculosis Anti-neoplastic or IM	Antibiotics [4, 5] HDS Cardiovascular
Top 5 agents	Flucloxacillin Erythromycin Disulfaram TMP/Sulfa Diclofenac	AM/CL Ebrotidine Anti-TB agents Ibuprofen Flutamide	AM/CL Nevirapine Atorvastatin Fenofibrate Ibuprofen	AM/CL Diclofenac Azathioprine Infliximab Nitrofurantion	Unknown HDS Rifampicin Traditional Chinese Med Isoniazid Pyrazinamide	AM/CL [4, 5] Isoniazid Nitrofurantoin TMP/Sulfa Minocycline

AM/CL, amoxicillin-clavulanate; *HDS*, herbal or dietary supplement; *IM*, immune modulators; *NSAIA*, non-steroidal anti-inflammatory agent; *TMP/Sulfa*, trimethoprim-sulfamethoxizole

*Not reported in paper. Data from https://www.citypopulation.de/php/france-nievre.php?cityid=58194. Predominantly Caucasian – Northern European

^ Not reported in paper. Data from https://www.worldatlas.com/articles/ethnic-groups-and-nationalities-in-iceland.html. Predominantly Caucasian – Northern European

~ Not reported in paper. Data from https://www.worldatlas.com/articles/largest-ethnic-minorities-in-spain.html

^^ Not reported in paper. Data from "Utrikes födda 2012: Fortsatt ökning av utrikes födda i Sverige" [Foreign born 2012: Further increase in foreign-born persons in Sweden]. Statistics Sweden, Unit for Population Statistics (in Swedish). 21 August 2013. Retrieved 12 March 2017

[6], and Europe [7–9]. Several are population based while others based on cohorts. While there are similarities in data, there are also remarkable differences in the estimated incidence, causative agents, and mortality.

Six relatively large studies are considered population based [1••, 5, 6, 8–10]. They report annual incidences that range from 2.4 to 23.8 per 100,000 persons (Table 1). Some gathered only inpatient cases, such that the incidences may be skewed toward more severe cases and underestimate the true incidence by missing outpatient cases. The studies from Iceland and France included both hospitalized and non-hospitalized and reported some of the higher incident rates of 19.1 and 13.9, respectively [6, 7]. Both studies included predominantly patients of northern European Caucasian descent. The Swedish registry of cases included only hospitalized cases and reported a lower rate of 2.4 [9]. On the other hand, a study of both outpatient and inpatient cases from the state of Delaware in the USA suggested an incidence of just 2.7 per 100,000 [5]. Here the cases were identified through gastroenterology practices only. In that study, the percentage of Caucasians reflected the US as a whole (70% versus 74%), but African Americans were over-represented at 22% versus 13%. The Spanish Registry is the oldest registry and draws cases from a population of predominantly Spanish natives, both inpatient and outpatient [8]. Despite having a relatively low threshold for enrollment of ALT over twice the upper limit of normal, they estimated one of the lowest incidences at 3.4 per 100,000.

The most recent study from China [1] stands in stark contrast to those from the USA, Europe, and Iceland (Table 1). It is the first population-based study to report on predominantly non-Caucasians, and it is by far the largest. At over 25,000 cases of DILI spanning just 3 years, the study dwarfs the others by over 30-fold. Its catchment included a remarkable 66 hospitals that had "complete capture" of cases and data. The 66 spanned every region of the country. Despite being limited to hospitalized patients, the incidence was the highest thus far reported at 23.8 per 100,000. The authors rightfully suggest that the true incidence is higher due to outpatient cases being missed.

Entry criteria were significantly different for the China study compared with others. The study from China had no liver biochemistry thresholds, relying only on codified discharge diagnoses suggesting DILI. Cases with a Roussel Uclaf Causality Assessment Method (RUCAM) [11] scores less than 6 (less than "probable") were generally excluded. Cases scoring less than 6 were reviewed by 3 hepatologists with expertise in DILII and only included in the analysis if at least 2 reviewers felt the case was probably DILI.

Thus, incidence estimates depend on how cases are defined and captured, but clearly there is variation across the globe and therefore across race and ethnicity. The study from China raises many questions about causal agents, genetics, and outcomes that may be unique to Asians and/or Han Chinese. Unfortunately, robust population based or registry data from other regions such as Africa and the Middle East remain absent.

Causal Classes and Agents

There are remarkable similarities in the classes and specific agents causing DILI, but also stark differences particularly comparing the data from China with the predominantly Caucasian populations studied previously (Table 1). Non-tuberculosis antimicrobials consistently predominate as a class of agents in studies from the USA, Iceland, and Europe. Except for the study from Sweden, all the western-based population studies list amoxicillin-clavulanate (AM/CL) as the most common individual agent. In Sweden, flucloxacillin is first and AM/CL does not make the top 5. The top remaining classes and agents reported in these studies vary but certain classes such as analgesics and NSAIAs, particularly diclofenac and ibuprofen, appear in these rankings more than once.

Again, the study from China stands in distinction. Herbal and dietary supplements (HDS) and traditional Chinese medications (TCM) top the list of classes and individual agents. As a class, HDS plus TCM accounted for 27% of cases. Anti-tuberculosis (TB) agents ranked second at 22%. Only 6% were due to non-tuberculosis antimicrobials, and this class did not make the top 3, coming in fourth behind anti-neoplastic or immune modulators (8%). This percent of non-TB antimicrobials is markedly lower than reported in the west. The US DILIN reported 40% of their cases were due to non-TB antimicrobials [4]. The Spanish DILI Registry most recently reported that antimicrobials accounted for 37% of their cases [12••]. Though not defined in this paper, probably more than half of these cases were due to non-TB agents [8].

Herbal and dietary supplement (HDS) use is on the rise in the west [13]. It accounted for just 16% in the US DILIN registry overall, but more recently, it has risen to 1 in 5 cases. Similarly, the Spanish DILI Registry recently reported HDS as the 6th most common class of agents overall since 1994, but by 2016, HDS had also risen to about 20% [12••]. These more recent rates are not so different from the data from China (27%), but the type of HDS products is likely different. Androgenic steroid injuries make up 35–38% of the HDS cases in the USA and Spain. By 2014–2016, androgenic steroid liver injury in Spain accounted for well over half of the non-conventional medicine liver injuries. Virtually, all DILI cases due to androgenic steroids or muscle building agents are in males [14, 15•]. Shen et al. make no mention of androgenic steroid injuries, and 60% of their HDS or TCM cases were in women, leading one to surmise that anabolic steroids or muscle building agents may not have been a major proportion of their HDS cases.

Besides the remarkable differences in causal agents described between Chinese and Caucasians, there are differences that also set African Americans (AA) apart. Chalasani et al. compared causative agents between 144 African Americans versus 841 Caucasians enrolled in the US DILIN [16••]. The most common agent for AAs was trimethoprim-sulfamethoxizole (TMP/Sulfa) at 7.6% of cases compared with 3.6% of cases for Caucasians. While amoxicillin-clavulanate (AM/CL) was the most common agent for Caucasians at 13.4%, it accounted for only 4.1% of AA cases. Phenytoin was also remarkably more common in AA DILI cases at 5% versus < 1% in Caucasians.

Outcomes

DILI outcome can be categorized into the three possibilities of complete recovery, chronic injury, or fatality (death or transplant). Chronic injury and long-term outcomes have been reviewed in a recent issue of *Current Hepatology Reports* [17], and there are little data on racial or regional differences for chronic injury. However, the studies from China and the US DILIN suggest acute (< 6 months) fatalities may vary by race [1, 16••]. AAs in the DILIN tended to have more severe DILI with 77% being hospitalized versus 58% for Caucasians ($p < 0.05$) [16••]. Median peak bilirubin (14.2 versus 12.7, $p = 0.06$), ALT (1117 versus 940, $p = 0.01$), and INR (1.9 versus 1.6, $p < 0.01$) were all higher as well. These differences translated to a higher fatality rate for AAs (10% versus 6%, $p = 0.02$).

Chinese patients with DILI also have some distinct differences in fatality risk. While studies from the west have generally found Hy's Law criteria (i.e., bilirubin > 2.5, ALT > 3× ULN, Alk phos < 2× ULN) to hold a roughly 10% positive predictive value for mortality [18–20], the data from China yielded a remarkably lower rate. Only 104 cases overall died or required liver transplantation, and there were 5,460 cases that met Hy's Law criteria. Even if we assume all 104 cases met Hy's Law and were included in the 5,460, the mortality rate remains 5-fold lower at 2%. The reasons for this difference are unclear. The authors mention that they may have less severe cases by not having a liver biochemistry threshold for inclusion, but this should not have affected the mortality rate when limited to those meeting Hy's Law. In China, various therapeutic agents are frequently applied to DILI cases. The authors do not define these therapies, but the possibility of life-saving DILI treatments in China is intriguing. The authors also cite their much lower transplant rate, implying that fatality as typically defined as death or liver transplant in western studies may have inflated the mortality rate. In other words, some patients transplanted for acute liver failure due to DILI may have been able to recover without transplant.

Background of Chronic Liver Disease

Pre-existing chronic liver disease varies by race and region. Whether such chronic liver disease creates a higher risk for DILI remains controversial [21]. Chronic hepatitis B and NAFLD are particularly noteworthy for their large but regionally disparate prevalences [22, 23]. Chronic hepatitis B is much more common in Asia and among Asian emigrants. In addition, the higher need for anti-tuberculosis medications in these populations has allowed several cohort studies looking at HBV infection as risk factor for DILI. Anti-tuberculosis medications, isoniazid in particularly, are among the most commonly reported and studied DILI agents. Individual studies yield conflicting results with some refuting [24, 25] and others supporting HBV as a risk for DILI [26–28]. Indeed, a recent meta-analysis came to the equivocal conclusion that HBV infection "may increase" the risk of liver injury from anti-tuberculosis medications [29]. When they examined all 15 studies meeting inclusion criteria, the odds ratio was 2.2 (95% confidence interval 1.4–3.4) in favor of HBV infection as a risk factor. However, if they tightened the DILI case definition, the association held only for the prospective studies. And when they restricted to studies with a strict DILI definition and only isoniazid, the association was lost.

Whether chronic hepatitis B is a risk factor for DILI in general is largely unknown but some information can be gleaned from the recent population-based DILI study by Shen et al. [1]. While they do not discuss hepatitis B as a risk factor per se, the prevalence of chronic HBV infection among their 25,927 cases was 12%, which is higher than the overall HBsAg seroprevalence of 7.2% in China based on 2006 data [30]. This background population prevalence is known to be falling and was presumably even lower by 2014 when Shen et al. gathered their cases. No multivariate comparison to determine HBV as an independent risk factor for DILI was generated from their data, but hopefully will be forthcoming in later cohort or case-control studies.

There are recent data for NAFLD as a risk factor for DILI which has large implications for DILI incidence. NAFLD is common in western, predominantly Caucasian countries and its incidence continues to rise. Bessone et al. postulate both biologic and epidemiologic plausibility for NAFLD as a risk for DILI [31]. They highlight certain drugs that cause liver injury by pathways that overlap with the pathophysiology of NAFLD. More importantly, authors point out that NAFLD patients with their associated metabolic syndrome tend toward polypharmacy which is associated with increased DILI risk [6]. A pharmacoepidemiologic study from Indiana reported a fourfold increased odds for the development of DILI from the top 10 hepatotoxic medications in the USA [32•]. A cohort study of 248 inpatients suggested a similar increased DILI risk for NAFLD patients [33].

Emigration from regions of higher to lower prevalences of hepatitis B will affect the epidemiology of DILI by region, but not so much by race. On the other hand, the rise of NAFLD within regions may have remarkable effects on race and DILI risk. Recent data suggest an increase in NAFLD in the Asia-Pacific region due to the rise in "urbanized lifestyle and dietary changes." [34] Whatever genetically based racial risk factors exist, such risk will be influenced by the rise of NAFLD, if for no other reason than the increased medication exposure that goes with the metabolic syndrome.

Genetics

Identifying genetic variants that increase the risk of DILI has been difficult because of the need for large numbers of bona fide cases. However, with maturation of several large registries of cases, genome-wide association studies (GWAS) have begun to show important results. The earliest breakthroughs have associated DILI from specific agents to certain HLA alleles, highlighting the probable role of the immune response in DILI. In a landmark study published in 2009, flucloxacillin DILI risk was found to be strongly associated with HLA-B*5701 [35]. Later, HLA-A*02:01 and HLA-DRB1*15.01 were found to be associated with in increased risk of amoxicillin-clavulanate (AM/CL) liver injury [36]. The latter finding is intriguing from a race standpoint because of the comparatively lower prevalence of AM/CL liver injury among African Americans discussed previously would coincide with the lower frequencies of these risk alleles compared with Caucasians [37, 38••]. Taken together, these data constitute one of the first possible genetic explanations for a racial difference in DILI risk.

The most recent study regarding genetics and DILI risk amplifies the theme of race and HLA association, and serves as an example of where GWAS studies in DILI will go in the future [39]. As with the study by Lucena et al. that links certain HLA haplotypes with AM/CL liver injury [36], the recent paper by Cirulli and Nicoletti, et al. utilize several separate registries of DILI cases, including the US DILIN, the International DILI consortium (iDILIC), and the registry of cases from Iceland. Without the growing number of well-characterized cases of DILI, GWAS studies have difficulty finding statistically significant associations. In this collaborative study, over 2000 cases of DILI were analyzed along with over 12,000 non-DILI controls. European, African-American, and Hispanic patient were included. Their findings were then validated in 113 cases and over 200,000 controls from Iceland. Such collaboration across continents was crucial.

With the increased number of cases and controls, the authors were able to identify a missense polymorphism (rs2476601) in the *PTPN22* gene that is associated with increased risk of DILI overall. This gene codes for a lymphoid tyrosine phosphate protein. The mechanism for increasing DILI risk is unclear but the frequency rs2476601 varies greatly across different populations. It appears in 15% of Finnish persons to as low as < 0.01% in East Asians. The risk association remained across races and regions despite this varied prevalence.

The lymphoid tyrosine phosphatase is expressed only in lymphoid cells and the rs2476601 missense has been previously associated with autoimmune disorders such as systemic lupus erythematosus, vitiligo, Grave's, and Behcet's, reinforcing the role of the immune response in DILI. Also, the penetrance of the risk seems affected by certain HLA haplotypes particularly for AM/CL liver injury cases. The odds ratio for risk over the entire study population was modest at 1.3, but it increased over 13-fold if the HLA haplotypes associated with AM/CL hepatotoxicity were present (HLA-A*02:01 and HLA-DRB1*15.01).

Such incremental increases in odds ratios by identifying combinations of genetic variants and HLA haplotypes bring the field closer to possible pre-treatment testing of patients to identify those at risk for liver injury. Such a 13-fold increased risk for AM/CL injury for those with the rs2476601, HLA-A*02:01 and HLA-DRB1*15.01 genotype begs the question of what population prevalence of this genetic profile must exist to make screening cost effective. One could envision tailored and targeted genetic screening for certain medications in particular races and populations based on background genetic risk. Such an approach would be particularly attractive and cost effective for medications that are used widely and can lead to significant morbidity and mortality when DILI does occur (e.g., isoniazid).

Conclusion

The field is entering an era of great promise for mitigating DILI across race and region. Large registries continue to grow across the globe bringing much needed diverse epidemiologic data. The recent study from China was a significant contribution in terms of sheer number of cases and counterbalancing the prior studies on US and European populations that are predominantly non-Hispanic or Hispanic Caucasians. Data on African Americans is just beginning to emerge from the USA. Such clinical data will be critical to informing further genetic studies that must take into account racial differences. The growing number of registry cases and collaboration will surely lead to landmark insights into DILI risk and pathophysiology by race.

However, challenges abound. It remains to be seen how cost effective and clinically useful genetic markers for risk will be. Such community effectiveness will be affected by a changing background of disease states and medications used. Hepatitis B prevalence is on the decline in certain countries

but not others. The rise of NAFLD will change the landscape across the globe, by changing the amount of medications prescribed and the population at risk of DILI overall. NAFLD could amplify the risk associated with certain genetic markers pathophysiologically. On the other hand, it may obfuscate identification of genetic markers by making it more difficult to identify true DILI cases for study. The acceleration of new medications approved and used for chronic liver diseases themselves will also challenge us to define injury and risk by race. How such changes will affect translation of genetic findings to clinical usefulness across races and regions remains to be seen.

Compliance with Ethical Standards

Conflict of Interest The author declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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