Editorial

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Drug-induced liver injury: Is it time for genetics to change our clinical practice?

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See Article, pages 1049–1053

Co-amoxiclav is a combination antibiotic containing amoxicillin trihydrate, a β-lactam antibiotic, with the potent β-lactamase inhibitor clavulanic acid. It is one of the most prescribed antibiotic worldwide both because of its large spectrum of action and for its general good safety. Amongst the possible side-effects of co-amoxiclav are diarrhea, vomiting, and thrush, which do not usually require medical attention. It can also induce allergic reactions and, as all antimicrobial agents, pseudomembranous colitis. Lastly, co-amoxiclav is known to have caused drug-induced liver injury (DILI) in some patients [1–3]. Although DILI is a very rare event, co-amoxiclav is one of the most common causes of DILI [2,3].

DILI is a rare idiosyncratic adverse drug reaction associated with commonly used drugs, mostly non-steroidal anti-inflammatory drugs, paracetamol, and antimicrobial agents [4,5]. Mainly because of the lack of internationally accepted criteria for DILI, data on the incidence of DILI cases are extremely variable [6,7]. It should be noted that half of the cases of acute liver failure are due to drug hepatotoxicity [4,5]. Recent major methodological and technological advances in many fields of basic science (i.e. the use of animals with various gene knockouts [8]) have contributed to a breakthrough in the understanding of the mechanisms underling DILI.

Based on the fact that a unique predisposition is required to develop a DILI, over the last few years several research groups have tried to understand the role of genetics in DILI [9]. However, the literature on DILI contains large numbers of publications that have attempted to identify the responsible genes by evaluating small numbers of single nucleotide polymorphisms in one or few specific candidate genes by means of case–control study designs [9]. Unfortunately, as in many other complex conditions (i.e. autoimmune diseases [10,11]), such approaches have led to few insights into the genetic basis of DILI, mainly because of its rarity and the consequent difficulty to find large numbers of affected individuals. A possible exception is the quite consistent findings of an association between the co-amoxiclav-induced liver injury and some human leukocyte antigen (HLA) alleles [12–15]. Indeed, an association has been reported between HLA-DRB1*15 and co-amoxiclav-related DILI in two out of three studies focused on this topic (Table 1) [12,13,15].

In the current issue of the Journal of Hepatology, Donaldson et al. [14] confirm the already known HLA association with DRB1*15 and also provide novel relevant data. In particular, they report a novel protective association with DRB1*07 within the HLA region [14]. The major strength of this study is the typing of the largest collection of DNA ($n = 61$) from patients with co-amoxiclav-related DILI (Table 1), and the inclusion, for the first time, of a control group of patients exposed to co-amoxiclav but showing no toxicity. We should note, however, that although the authors must be commended for their enormous multicentric effort in collecting DNA from this very rare condition, 61 cases is a small series to be typed in a genetic association study. Furthermore, the results herein, similar to other gene descriptions in DILI patients, do not include functional analysis.

The publication of the first high-density genome-wide association study (GWAS) in cases with DILI due to an antimicrobial agent, flucloxacillin [16], has now opened a new era in the field of DILI which will surely allow substantial advances in our mechanistic understanding of DILI [9]. It should be noted that this first GWAS identified HLA variants as risk factors for liver toxicity due to flucloxacillin. Although it has been suggested that genetic associations for DILI are generally drug specific [9], the HLA class I and II genes are emerging as major players in the predisposition to most forms of DILI [9]. HLA genes play a crucial role in the host immune response because they are involved in antigen presentation [17,18]. For this reason, the immunologic idiosyncrasy may be mediated by the HLA system and DILI may be linked with certain HLA genes [9]. Unfortunately, since Donaldson et al. did not perform a GWAS with their unique collection of DNA, their current candidate gene study can only confirm the role of HLA genes in co-amoxiclav-related liver toxicity, but it cannot exclude that other genes also have a role in the predisposition to this form of DILI [14].

The main aim of genetic studies on DILI is their contribution in aiding prediction in individual patients [19], in line with the rapid advances in genetics-based personalized medicine. The issue is of major clinical relevance and the expectation is very high [5]. However, because the current first wave of GWAS allows for the identification of only rare genetic variants [11] and because

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Editorial

Table 1. Reported HLA associations in co-amoxiclav-induced liver injury.

Years	Country	HLA investigated	Significant association with	Prevalence in co-amoxiclav DILI *(n)*	Prevalence in controls *(n)*	Corrected *p* value	[Ref.]
1999	Belgium	A, B, DRB, DQB	DRB1*1501	57% (20/35)	15% (9/60)	<0.003	[12]
			DRB5*0101	57% (20/35)	15% (9/60)	<0.003	
			DQB1*0602	57% (20/35)	12% (7/60)	<0.0005	
2000	U.K.	DRB, DQA, DQB, DPB	DRB1*1501	67% (12/18)	20% (27/134)	<0.0002	[13]
2004	Spain	DRB, DQB	No Associations	27 cases	600 controls	-	[15]
2010	U.K.	DRB1, DQB1	DRB1*1501	53% (32/61)	30% (57/191)	0.002	[14]
			DRB1*07	10% (6/61)	29% (56/191)	0.03	

DILI is a very rare condition [5], the initial insights into genetic factors affecting DILI susceptibility do not require the establishment of genetic screening tests that will guide and/or change clinical practice. Considering the study by Donaldson et al. [14], shall we perform the HLA mapping in all patients who have to be treated with co-amoxiclav? Would we prescribe co-amoxiclav to subjects who have HLA DRB1*15? I suspect that we are moving in the right direction, but these questions will require more time to be answered.

Conflicts of interest

The author declared that the he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] van den Broek JW, Buennemeyer BL, Stricker BH. Cholestatic hepatitis caused by a combination of amoxicillin and clavulanic acid (Augmentin). Ned Tijdschr Geneeskd 1988;132:1495–1497.
[2] Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129: 512–521.
[3] Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008;135: 1924–1934 (1934 e1921–1924).
[4] Kaplowitz N. Idiosyncratic drug hepatotoxicity. Nat Rev Drug Discov 2005;4:489–499.
[5] Verma S, Kaplowitz N. Diagnosis, management and prevention of drug-induced liver injury. Gut 2009;58:1555–1564.
[6] Meier Y, Cavallaro M, Roos M, Pauli-Magnus C, Folkers G, Meier PJ, et al. Incidence of drug-induced liver injury in medical inpatients. Eur J Clin Pharmacol 2005;61:135–143.
[7] Sgro C, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology 2002;36:451–455.
[8] Ong MM, Latchoumycandane C, Boelsterli UA. Troglitazone-induced hepatic necrosis in an animal model of silent genetic mitochondrial abnormalities. Toxicol Sci 2007;97:205–213.
[9] Daly AK, Day CP. Genetic association studies in drug-induced liver injury. Semin Liver Dis 2009;29:400–411.
[10] Invernizzi P. Future directions in genetic for autoimmune diseases. J Autoimmun 2009;33:1–2.
[11] Invernizzi P, Gershwin ME. The genetics of human autoimmune disease. J Autoimmun 2009;33:290–299.
[12] Hautekeete ML, Horsmans Y, Van Waeyenberge C, Demanet C, Henrion J, Verbist L, et al. HLA association of amoxicillin–clavulanate-induced hepatitis. Gastroenterology 1999;117:1181–1186.
[13] O'Donohue J, Oien KA, Donaldson P, Underhill J, Clare M, MacSween RN, et al. Co-amoxiclav jaundice: clinical and histological features and HLA class II association. Gut 2000;47:717–720.
[14] Donaldson PT, Daly AK, Henderson J, Graham J, Pirmohamed M, Bernal W, et al. Human leucocyte antigen class II genotype in susceptibility and resistance to co-amoxiclav-induced liver injury. J Hepatol 2010;53: 1049–1053.
[15] Andrade RJ, Lucena MI, Alonso A, Garcia-Cortes M, Garcia-Ruiz E, Benitez R, et al. HLA class II genotype influences the type of liver injury in drug-induced idiosyncratic liver disease. Hepatology 2004;39:1603–1612.
[16] Daly AK, Donaldson PT, Bhatnagar P, Shen Y, Pe'er I, Floratos A, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nat Genet 2009;41:816–819.
[17] Klein J, Sato A. The HLA system. First of two parts. N Engl J Med 2000;343:702–709.
[18] Klein J, Sato A. The HLA system. Second of two parts. N Engl J Med 2000;343:782–786.
[19] Russmann S, Jetter A, Kullak-Ublick GA. Pharmacogenetics of drug-induced liver injury. Hepatology 2010;52:748–761.