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SAFETY OF FLUCLOXACILLIN IN HIV-INFECTED PATIENTS WITH POSITIVE HLA-B*5701 GENOTYPE

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BACKGROUND

- Flucloxacillin is a semi-synthetic penicillin, widely used for the management of soft-tissue infections has been associated with drug-induced liver injury (DILI)
- A recent study using genome-wide association (GWA) methods identified the presence of the HLA-B*5701 allele to be associated with a high risk of DILI (odds ratio= 80.6, *P*=8.7 x10^{-33})[1] with the conclusion that HLA-B*5701 may be the main genetic risk factor for flucloxacillin-induced liver injury
- HLA-B*5701 screening is routinely performed to identify HIV-infected individuals at risk of hypersensitivity reaction (HSR) to the antiretroviral drug, abacavir. As a result, HLA-B*5701 testing is now a routine part of care in many HIV clinics
- Given the high prevalence of soft-tissue infections in HIV-1 positive patients, we investigated whether flucloxacillin use was associated with adverse events in a cohort of HIV-infected individuals known to be HLA-B*5701 positive.

METHODS

- Clinical and pharmacological prospective databases from HIV-infected patients attending the HIV department at St Mary's Hospital in London were used to identify individuals who had tested positive for the HLA-B*5701 allele using a commercial polymerase chain reaction assay (Lab21 Ltd., Cambridge, UK) between January 2008 and July 2012
- Clinical and laboratory parameters such as alanine aminotransferase (ALT), bilirubin and alkaline phosphatase (Alk Phos) were assessed in those individuals with a positive HLA-B*5701 test who had a documented course of flucloxacillin during the study period

RESULTS (1)

TABLE 1. Patient demographics

Clinical parameter	All
Female Male	1 (10%) 9 (90%)
Age, mean years (SD)	51 (2)
Ethnicity	
White Black African	9 (90%) 1 (10%)
CD4 count in cells/mL (SD)	572 (146)
Uninfected Infected	31 (93%) 2 (6%)
cART	10 (100%)
PI based NNRTI based	6 (60%) 4 (40%)

cART: combine antiretroviral therapy; PI: protease inhibitor, NNRTI: Non- nucleoside reverse transcriptase inhibitor

- We identified 79 individuals who had tested positive for the HLA B*5701. In total 10 of 79 (12.7%) had received flucloxacillin during the study period
- In all cases, flucloxacillin was prescribed for uncomplicated soft-tissue infections. The median total dose and duration of treatment were 20 gr (range 10 – 28 g) and 10 days (range 5 – 14 days), respectively.

RESULTS (2):

- After reviewing all available clinical and laboratory information, no case of suspected or confirmed clinical or biochemical toxicities within 1–90 days after prescription of flucloxacillin were identified
- Liver function tests were within normal limits apart from in the one case with HCV infection, in which ALT before and after the 90 days of observation remained above 60(IU/l)
- The interval of 1 – 90 days after prescription was chosen because of the characteristic clinical picture of flucloxacillin-DILI described in clinical reports of liver disease associated with flucloxacillin

TABLE 2. Characteristics of all included cases

Case	Age	Sex	Treatment duration(days)	Total dose(gr)	Indication
1	47	M	5	5	Folliculitis
2	50	M	14	28	Cellulitis
3	50	M	5	5	Boil
4	53	M	5	5	Skin infection
5	54	M	7	7	Folliculitis
6	50	F	14	14	Boil abscess
7	54	M	14	14	Boil/ abscess
8	49	M	7	7	Folliculitis
9	53	M	7	7	Toe infection
10	51	M	10	10	Skin infection

DISCUSSION

- Despite the recently reported association between HLA-B*5071 and flucloxacillin DILI from a case control study[1], we found no evidence of liver toxicity in a small sample of HIV-infected patients treated with flucloxacillin and carrying both the HLA- B*5701 allele and receiving flucloxacillin.
- Although these data suggest that there may not be a major risk to HIV patients in routine practice, a note of caution needs to be added. Firstly, age over 55 years old, female sex and a treatment duration longer than 14 days have been proposed as risk factors for flucloxacillin DILI[2]. In this study, all patients were below the age of 55 years, only one was a woman and none had more than 14 days of flucloxacillin therapy. Therefore is not possible to conclude that having a HLA-B*5071 genotype is not associated with flucloxacillin DILI in all HIV-1 positive individuals.
- It remains crucial for clinicians to be aware of the association of HLA-B*5701 with DILI, particularly in elderly patients, those with underlying liver disease and those requiring prolonged antibiotic therapy.
- However, as flucloxicillin remains the treatment of choice of methicillin sensitive Staphylococcus auerus (MSSA) infections in the UK. We recommend for HLA-B*5701 positive HIV patients with MSSA infections, to initiate flucloxacillin with careful monitoring of liver function parameters. If they develop biochemical evidence of hepatitis, the drug should be stopped immediately

REFERENCES

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