



HAL
open science

Existence of a relationship between increased serum alanine aminotransferase levels (ALT) detected in premarketing clinical trials and postmarketing published hepatotoxicity case-reports

Lucia Llanos, Rocio Moreu, Teresa Ortin, Ana Peiro, Sonia Pascual, Pablo Bellot, Claudia Barquero, Ruben Frances, José Such, Miguel Pérez-Mateo, et al.

► To cite this version:

Lucia Llanos, Rocio Moreu, Teresa Ortin, Ana Peiro, Sonia Pascual, et al.. Existence of a relationship between increased serum alanine aminotransferase levels (ALT) detected in premarketing clinical trials and postmarketing published hepatotoxicity case-reports. *Alimentary Pharmacology and Therapeutics*, 2010, 31 (12), pp.1337. 10.1111/j.1365-2036.2010.04298.x . hal-00552548

HAL Id: hal-00552548

<https://hal.science/hal-00552548>

Submitted on 6 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Existence of a relationship between increased serum alanine aminotransferase levels (ALT) detected in premarketing clinical trials and postmarketing published hepatotoxicity case-reports

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0934-2009.R1
Manuscript Type:	Original Scientific Paper
Date Submitted by the Author:	08-Mar-2010
Complete List of Authors:	Llanos, Lucia; Hospital General Universitario de Alicante, Clinical Pharmacology Section Moreu, Rocio; Hospital General Universitario de Alicante, Clinical Pharmacology Section Ortin, Teresa; Hospital General Universitario de Alicante, Clinical Pharmacology Section Peiro, Ana; Hospital General Universitario de Alicante, Clinical Pharmacology Section; Universidad Miguel Hernandez, Instituto de Bioingeniería pascual, sonia; Hospital General Universitario de Alicante, Liver Unit; Instituto de Salud Carlos III, CIBERehd Bellot, Pablo; Hospital General Universitario de Alicante, Liver Unit Barquero, Claudia; Hospital General Universitario de Alicante, Liver Unit Frances, Ruben; Instituto de Salud Carlos III, CIBERehd Such, José; Instituto de Salud Carlos III, CIBERehd; Hospital General Universitario, Liver Unit Pérez-Mateo, Miguel; Hospital General Universitario de Alicante, Liver Unit Horga, Jose F; Hospital General Universitario de Alicante, Clinical Pharmacology Section; Universidad Miguel Hernandez, Instituto de Bioingeniería Zapater, Pedro; Hospital General Universitario de Alicante, Clinical Pharmacology Section; Instituto de Salud Carlos III, CIBERehd; Universidad Miguel Hernandez, Instituto de Bioingeniería
Keywords:	Drug-induced liver disease < Hepatology, Liver function tests < Hepatology, Clinical pharmacology < Topics, Epidemiology < Topics

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



For Peer Review

Title Page:**Existence of a relationship between increased serum alanine aminotransferase levels (ALT) detected in premarketing clinical trials and postmarketing published hepatotoxicity case-reports.**

Lucía Llanos¹, Rocío Moreu¹, Teresa Ortin¹, Ana M Peiró^{1,4}, Sonia Pascual^{2,3}, Pablo Bellot^{2,3}, Claudia Barquero², Rubén Francés^{2,3}, José Such^{2,3}, Miguel Pérez-Mateo², José F. Horga^{1,4}, Pedro Zapater^{1,3,4}.

1- Clinical Pharmacology Section. Hospital General Universitario, Alicante, Spain.

2- Liver Unit. Hospital General Universitario, Alicante, Spain.

3- CIBERehd, Instituto de Salud Carlos III, Madrid, Spain.

4-Instituto de Bioingeniería. Universidad Miguel Hernández, Elche, Alicante, Spain.

CONDENSED RUNNING TITLE:

Hepatotoxicity, ALT levels and DILI case-reports

KEY WORDS:

CORRESPONDENCE AND REPRINT REQUESTS: Pedro Zapater. Sección de Farmacología Clínica. Hospital General Universitario, Alicante. C/ Pintor Baeza, 12. 03550. Alicante. SPAIN.

Tel: 965938226. Fax: 965938226 e-mail: zapater_ped@gva.es

Summary

Background: Drug-induced Liver Injury (DILI) profile in most drugs' available information is based on both the incidence of **ALT** elevations in clinical trials and published case reports. **Aim:** to assess the relationship between ALT elevations in clinical trials and the number of published case reports in the postmarketing setting. **Methods:** hepatotoxic drugs were identified from product labelling and classified in High-medium risk (Black Box Warning or Precautions section) or low risk (a statement in the Adverse Reactions section). Incidence of **ALT** elevations ($\geq 3 \times \text{ULN}$) for drug (I_D) and placebo (I_P) treated patients in premarketing clinical trials and DILI published case-reports were retrieved from product labelling **and Medline**. **Results:** Median I_P was 10/1000. High-medium risk drugs median I_D was significantly higher compared to low risk drugs (17/1000 vs 10/1000; $p=0.046$). Chi-square test, absolute difference and Odds Ratio comparing I_D and I_P identified 35%, 51% and 77% of high-medium risk drugs, respectively. Less number of case-reports were associated with low than high-medium risk drugs (1vs7; $p=0.001$). High Odds Ratio in clinical trials (I_D vs I_P) was the strongest predictor of published DILI case-reports. **Conclusion:** A relationship between increased ALT incidence in premarketing clinical trials and postmarketing published case reports exists.

Introduction

Drug-induced Liver Injury (DILI) is the most common reason cited for withdrawal of an approved drug^{1, 2}. Forty-two percent of postmarketing DILI events are not detected in studies in animal models³ and only rarely in clinical trials in humans mostly due to insufficient statistical power to detect serious adverse reactions that may occur infrequently⁴.

Identification of hepatotoxicity cases in premarketing clinical trials is based on elevations of alanine aminotransferase (ALT) and bilirubin above the upper limits of normal (ULN)². However similar elevations have been also reported in patients and healthy volunteers receiving placebo⁵. Accordingly, it has become a standard practice to look for elevations of ALT 3 or 5 times above ULN (ALT >3xULN or >5xULN).

Since this same increase of ALT values may be found in 0.1-1.0% of placebo-treated patients included in clinical trials, only rates higher than 2-3% have been considered as a possible warning signal in patients receiving an investigational drug. Even so, the value of this increase remains into question since two different scenarios have been detected: while certain drugs such as statins, tacrine or aspirin presenting such rates of ALT increases in clinical trials have proven safe after marketing^{6,7}, other drugs such as bromfenac, dilevalol, troglitazone, and trovafloxacin that presented similar increases in premarketing studies were finally followed by reports of cases of fulminant hepatitis among patients treated with these drugs, information that ultimately led to their removal from the market^{2,8-11}. Therefore, the true meaning of ALT and bilirubin elevations in clinical trials and their correlation with the subsequent development of clinically significant DILI remains an open issue.

Once a drug is marketed though, information about risk of hepatotoxicity comes mainly from phase IV clinical trials, adverse reactions spontaneous reporting systems and published case-reports or case series. The latter, although widely criticized due to their well known limitations and biases¹², represent about one-third of the published literature on adverse drug reactions¹³. Moreover, case

1
2
3 reports have been identified as the most important source of information that
4 finally may lead to withdraw a drug from the market for safety reasons¹⁴.
5
6
7

8
9 DILI profile in most drugs' available information is based on both the incidence
10 of elevations of ALT in clinical trials and published case reports. To the best of
11 our knowledge, the relationship between these two sources of information has
12 not been studied. The aim of this investigation has been to assess the value of
13 ALT elevations in clinical trials as predictors of the development of
14 hepatotoxicity, expressed as the number of published case reports in the
15 postmarketing setting.
16
17
18
19
20
21

22 Methods

23
24
25 Identification of drugs showing elevations of ALT 3 times above ULN (ALT
26 >3xULN) in clinical trials: we used the search tool available in 2007 Physicians'
27 Desk Reference (PDR 2007) to identify potentially hepatotoxic drugs. For the
28 purpose of this study, a 'hepatotoxic drug' was defined as a prescription drug for
29 which the terms [(hepatic enzymes elevated) OR (hepatotoxicity) OR (elevated
30 aminotransferases) OR (liver injury) OR (hepatic dysfunction) OR (increased
31 SGPT) OR (liver damage) OR (elevated ALT) OR (elevated serum
32 transaminases) OR (liver test abnormalities) OR (hepatic/liver failure) OR
33 (hepatic/liver necrosis)] were explicitly stated in product labelling. Drugs
34 indicated for the treatment of hepatitis B or C, antineoplastic agents, products
35 containing more than one active ingredient, hormones, vitamins, blood
36 derivatives and topic drugs were excluded.
37
38
39
40
41
42
43
44
45
46
47
48
49

50 Information on the incidence of elevations of ALT ($\geq 3 \times \text{ULN}$) for drug-treated and
51 placebo-treated patients (I_D and I_C , respectively) was retrieved either from
52 product labelling, Food and Drug Administration (FDA) or European Medicines
53 Agency (EMA) assessment or review reports. A Pubmed search was also
54 performed to look for placebo controlled clinical trials or meta-analysis, using the
55 limits "All Adult: 19+ years, Comparative Study, Humans". When no information
56 about the number of drug-treated and placebo-treated patients with ALT
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

$\geq 3xULN$ was available but the product labelling made an unspecific asseveration like "*incidence ≤ 0.01* ", this maximal incidence was recorded and the number of patients with ALT $\geq 3xULN$ calculated from total number of drug treated patients.

Levels of hepatotoxicity risk: according to safety information included in the product labelling, a drug was defined as having a) high-medium level of risk if there was specific information included as a Black Box Warning or in the Precautions section and b) low level of risk if only a statement about hepatotoxicity was listed in the Adverse Reactions section¹⁵.

Published DILI-case reports: Publications of DILI case-reports for each drug included in the study were searched in Pubmed from 1964 to december 2008 using the limits: "Humans, Case Reports" and the terms ("Hepatitis, Toxic"[Mesh] AND *drug name*) OR ("hepatotoxicity" AND *drug name*) OR ("Drug induced liver disease" AND *drug name*). To complete the search, references from review manuscripts and hepatotoxicity books were also consulted. For each included drug, number of published DILI case reports and years of publication were registered.

Time "at risk" of causing hepatotoxicity: to estimate the time (in years) of drug availability on the market we calculated the following two figures: a) years from the first publication of an article in Pubmed (where the drug was administered to humans) to December 2008 and b) years from the first approval by a regulatory agency (FDA, The European Medicines Agency (EMA) or the Spanish Agency of Medicines before EMA was created) to December 2008 or, where appropriated, to the year when the drug was withdrawn for any reason from the market.

Statistical methods: drug and placebo incidences (I_D and I_C) of ALT $\geq 3xULN$ were compared between high-medium and low risk drugs using three different strategies: a) Chi square test with Yates's correction as needed, b) absolute differences of incidences or Excess Risk calculated as $I_D - I_C$, and c) Odds Ratio (PrO) calculated as $PrO = (K_d - K_c) / K_c$, where K_d and K_c are the maximum number of occurrences of ALT $\geq 3xULN$ episodes that could be detected with a probability of 0.05 or higher in a population of drug or placebo-

1
2
3 treated patients, respectively, assuming a sample size equal to the number of
4 drug-treated patients in placebo-controlled clinical trials. Probability of K values
5 was calculated using a Poisson's distribution estimated using incidence I_C and I_D
6 values as expected number of occurrences in a time-interval of given length or λ
7 values¹⁶.
8
9

10
11
12
13 Chi square test results were dichotomized in non significant or significant
14 according to p value \geq or $<$ 0.05. Excess Risk ($I_D - I_C$) and PrO were
15 dichotomized in no relevant or relevant result according to value \leq or $>$ upper
16 quartile (75th percentile) calculated in the low risk group of drugs.
17
18

19
20
21 Number of published case reports and rate of case reports published by year
22 were categorized in three groups: $<$ 25th percentile, between 25th and 75th
23 percentiles and $>$ 75th percentile.
24
25

26
27
28 Quantitative data are described as median and interquartile range (IQR).
29 Qualitative data are described as frequencies or percentages with 95%
30 confidence intervals calculated using the binomial distribution. Differences
31 between groups were analyzed through the U-Mann-Whitney non-parametrical
32 test for quantitative variables and the Chi-square test for qualitative ones. A
33 difference was considered significant if $p < 0.05$. All statistical analysis was
34 performed using SPSS 14.0 software.
35
36
37
38
39
40

41 **Results**

42
43
44 A total of 204 potentially hepatotoxic active substances were retrieved. Thirty-
45 eight of them were excluded because the product information indicated only the
46 need for dose adjusting in hepatic insufficiency. Five were excluded due to their
47 indication for therapy of patients with chronic hepatitis B or C virus infection. A
48 hundred and sixty one drugs were finally selected, but sufficient information to
49 calculate the incidence of ALT elevations $\geq 3 \times \text{ULN}$ in treatment and placebo
50 groups was available only for 67 active substances (42%). Four of them
51 (pergolide, efalizumab, rofecoxib and valdecoxib) had been withdrawn from the
52 market due to safety reasons other than hepatotoxicity by the time this study was
53 performed. Table 1 show a list of these drugs, the number of drug-treated and
54
55
56
57
58
59
60

1
2
3 placebo-treated patients (N_D and N_C , respectively) and their corresponding
4 incidences (I_C and I_D , respectively).
5
6

7
8 According to level of risk, 37 drugs were classified as having high-medium risk
9 and 30 as having low hepatotoxicity risk. As shown in Figure 1.A), there were no
10 significant differences between the total number of patients included in drug and
11 placebo groups in clinical trials either for high-medium risk drugs or low risk
12 drugs ($p=0.097$ for N_C , $p=0.528$ for N_D).
13
14
15
16

17
18 Median incidence of ALT elevations $\geq 3xULN$ in placebo-treated patients (I_C) was
19 10/1000 (IQR 3-16/1000; figure 1.B) for both high-medium and low risk groups,
20 this finding being consistent with previously reported data^{2,5}.
21
22
23

24
25 A higher incidence of ALT elevations $\geq 3xULN$ was observed for patients treated
26 with high-medium risk drugs (median 17/1000; IQR 7-40/1000) compared to
27 patients treated with low risk drugs (median 10/1000; IQR 7-12/1000; Figure 1.
28 B; $p=0.046$). This significant difference in I_D was also observed when $I_D - I_C$ and
29 PrO were calculated (Figures 1.B y 1.C). Patients treated with high-medium risk
30 drugs showed an increase of risk of 7/1000 (IQR 1-20/1000) with respect to
31 placebo treated patients, being significantly higher than the increase shown by
32 patients in the low risk drugs (1/1000; IQR: 0-6 /1000; $p=0.001$). Median PrO
33 value for patients treated with high-medium risk drugs (0.6; IQR 0.26-1.61,
34 equivalent to a probability of 37.5%; IQR 20.6-61.7%) was significantly higher
35 compared with patients treated with low risk drugs (0.0; IQR: 0.0-0.25,
36 equivalent to a probability of 0%; IQR 0.0-20.0%; $p = 0.001$).
37
38
39
40
41
42
43
44
45

46
47 When incidences of ALT elevations observed in drug-treated and placebo-
48 treated patients were compared through a Chi Square test (Figure 2A)
49 statistically significant differences ($p<0.05$) were observed only for 13 out of 37
50 high-medium risk drugs (35%) and for 1 out of 30 low risk drugs (3%; $p=0.020$).
51 In contrast, if Excess of Risk ($I_D - I_C$) was categorized establishing as relevant
52 any value higher than the 75th percentile for low risk drugs (0.006), up to 51%
53 high-medium risk drugs were identified as having a relevant increase of ALT
54 elevations, compared to 20% in the low risk group ($p=0.011$; Figure 2.B). The
55
56
57
58
59
60

1
2
3 use of a higher cut-off point (0.008, 0.010) decreases the number of high-
4 medium risk drugs identified to 43% and 38%, respectively.
5
6

7
8 In addition, PrO was categorized from the observation that in the low risk group
9 of drugs the value corresponding to 75th percentile was 0.25, equivalent to a
10 20% probability. Higher excess of risk values were defined as relevant.
11 According to this, up to 77% of high-medium risk drugs show differences greater
12 than or equal 20%, compared to 22% of low risk drugs ($p=0.001$).
13
14
15
16

17 *Time "at risk" and number of case-reports*

18
19
20 A median of 18 years (IQR: 13-28) had passed from the first publication date
21 and 13 years (IQR: 10-20) from the first marketing authorization date for the 67
22 studied drugs. There were no significant differences between high-medium risk
23 drugs and low risk drugs in time from the first publication in humans (Median 18;
24 IQR 14-17 vs 18; IQR 13-28, $p=0.965$) or time from the first marketing
25 authorization (Median 13; IQR 10-19 vs 12; IQR 10-21, $p=0.695$).
26
27
28
29
30
31

32 The number of case reports was categorized in accordance with percentiles
33 25th and 75th values in three groups: $n \leq 1$, $1 > n \leq 9$, $n > 9$. There was a significantly
34 higher number of published case reports for high-medium risk drugs (median 7;
35 IQR 2-12) than for low risk ones (median 1; IQR 0-2; $p=0.001$). Frequencies of
36 distribution of number of case reports stratified by levels of risk are shown in
37 figure 3.A). While most of the low risk drugs are associated with less than 1
38 case report, it is much more frequent that high-medium risk drugs have between
39 1 and 9, or even more than 9 published case reports ($p= 0.001$).
40
41
42
43
44
45
46

47 *Relationship between clinical trials data and case reports*

48
49
50 No significant differences were observed in the number of published cases
51 between drugs that had shown a significant difference in the incidence of ALT as
52 compared to those drugs which had not (Figure 3.B). Similarly, no relevant
53 differences were observed in the number of published cases for drugs with a
54 **higher** excess risk compared to drugs with a lower excess risk (Figure 3.C).
55 However, those drugs with a relevant difference according to the PrO value
56
57
58
59
60

1
2
3 were significantly associated with a higher number of published case reports
4 (Figure 3.D; $p=0.020$).
5
6
7
8
9

10 Discussion

11
12
13 In this investigation we show evidences of a relationship between drug-induced
14 serum ALT elevations in premarketing studies and the number of DILI case-
15 reports published in the postmarketing setting.
16
17
18

19
20 The current characterization of a drug's hepatotoxic profile relies **mainly** on
21 information of ALT elevations from premarketing clinical trials and case reports
22 published in scientific literature in the post authorization period. **So far**, the
23 detection of ALT increments during premarketing trials may not be
24 systematically followed by relevant clinical consequences. Then the predictive
25 usefulness of this parameter for estimation of future cases of hepatotoxicity has
26 been widely debated and other strategies have been proposed^{17,18}.
27
28
29
30
31
32
33

34 Indeed, we have observed that the labelling of approximately 60% of the drugs
35 here evaluated that are considered as potentially hepatotoxic does not include
36 information regarding the frequency of ALT elevations in premarketing clinical
37 trials, suggesting that analytical and clinical evidences other than ALT elevations
38 were considered in the drug labelling procedure.
39
40
41
42
43
44

45 We have not detected statistically significant differences among placebo-treated
46 patients irrespective of the clinical trial where **they** had been included (Fig 1) nor
47 between drug and placebo-treated patients in up to 65% of the high-medium risk
48 drugs for hepatotoxicity (Fig 2A). In contrast, a 7-fold higher excess of risk, as
49 determined by $I_D - I_C$ and PrO, for high-medium risk drugs was observed (Fig.
50 2B,C), suggesting that these drugs are indeed significantly associated with a
51 higher incidence of ALT elevations in premarketing clinical trials but that
52 conventional statistical approaches are powerless to detect such differences.
53 However, methods that put in relation drug and placebo corresponding risks
54 may be more sensitive in detecting these differences.
55
56
57
58
59
60

1
2
3 In **spite of** what has been considered regarding the low predicting value for
4 hepatotoxicity of premarketing elevated ALT for a given drug¹⁷, our study shows
5 that this fact is indeed associated with an increased number of postmarketing
6 published DILI case reports (Fig 3), suggesting that ALT increases, albeit
7 infrequent, may predict the development of clinically serious DILI. Accordingly,
8 the systematic reporting of incidence of ALT elevations in phase III clinical trial
9 reports should be encouraged.
10
11
12
13
14
15

16
17 Our study has several limitations to consider. First is the lack of available
18 information on incidence of ALT elevations in most placebo-controlled clinical
19 trials. This may be explained at least in part because criteria **used by** regulatory
20 agencies to assess a drug's liver safety profile may be based on preclinical
21 toxicity data or in available information from other drugs of the same
22 pharmacological group.
23
24
25
26
27

28 **Second, we have classified hepatotoxicity risk of drugs according to product**
29 **labelling as has been described elsewhere¹⁵. Through this approach, it is**
30 **obviously not possible to discriminate the mechanism of injury for each drug**
31 **(dose dependent *versus* idiosyncratic). So far most hepatotoxic drugs that have**
32 **been withdrawn from the market (bromfenac, dilevalol, troglitazone, and**
33 **trovafloxacin) were because of idiosyncratic dose independent DILI ^{2, 8-11}. It has**
34 **been suggested that idiosyncratic DILI often occur on a background, higher rate**
35 **of mild, asymptomatic, and usually transient liver injury, detected as abnormal**
36 **ALT levels suggesting that the drug has a mild toxic potential but in rare**
37 **individuals this potential leads to metabolism-dependent hypersensitivity**
38 **influenced by genetic and or/ environmental factors¹⁹. Then, the relationship**
39 **observed in our study between rate of abnormal ALT levels in clinical trials and**
40 **postmarketing DILI case-reports could be linked to detection of drugs with mild**
41 **toxic potential that in some susceptible individuals may trigger a serious**
42 **reaction. However, we cannot exclude that they are independent phenomena.**
43 **Another type of study (long-term prospective follow-up of patients with abnormal**
44 **ALT values in clinical trials and experimental studies in animal models) is**
45 **needed to explain the mechanism and causes of this association takes place.**
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Third, criteria used by regulatory agencies to establish warnings or precautions in the product labelling often include information from published case reports or spontaneously notified adverse reactions in the postmarketing period. Thus, the finding of a significantly higher number of published case reports may have been influenced by the previous labelling as high-medium risk drugs, a possibility that we cannot exclude.. Nevertheless, as far as we know this is the first time that a significant association between the incidence of ALT elevations in premarketing clinical trials and the number of published case reports is reported..

On the other hand, we have used the number of published DILI-case reports as an indicator of hepatotoxicity potential of a drug. Publication of case-reports is a process subjected to multiple bias and limitations¹⁴: under-reporting, subjective causality evaluation²⁰, preferential report of cases with recent-marketed drugs or special clinical characteristics, disparity and frequent scarce of data. Despite all these limitations, information from published case-reports represents a significant portion of the information provided by referral sources in DILI (books, reviews).

A systematic register of postmarketing adverse drug reactions in an accessible database would also be desirable to overcome this drawback.

In conclusion, our study shows a significant relationship between ALT elevations observed in premarketing phase III placebo-controlled clinical trials and postmarketing published DILI case-reports. Thus, significant increases in serum ALT elevations in clinical trials detected by means of adequate statistical approaches would be useful to include accurate risk information in the labelling process of a drug and to establish a closer monitoring schedule to predict hepatotoxicity once the drug is in the market.

1
2
3 *None of the authors of this article have any conflicts of interest to declare.*
4
5

6
7 **Acknowledge**
8

9
10 This work was supported in part with grants from the Plan Nacional de I+D,
11 Instituto de Salud Carlos III (PI04/0186) Madrid, Spain, and Fundación de
12 Investigación de Hospital General Universitario de Alicante.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

Table 1 - Potentially hepatotoxic drugs including information about ALT elevations in drug labeling.

Low Risk					High-Medium Risk				
Drug	N _c	I _c	N _D	I _D	Drug	N _c	I _c	N _D	I _D
Acamprosate	774	0,012	968	0,011	Acarbose	999	0,010	1255	0,030
Acyclovir	547	0,015	508	0,020	Alefacept	114	0,079	122	0,172
Alosetron	2363	0,012	8328	0,010	Amiodarone	1758	0,008	1782	0,017
Alprazolam	1231	0,018	1388	0,032	Atorvastatin	270	0,004	4271	0,007
Aripiprazole	341	0,006	763	0,007	Bosentan	288	0,021	677	0,061
Cevimeline	161	0,043	829	0,046	Celecoxib	4084	0,003	12750	0,004
Citalopram	386	0,003	941	0,003	Diclofenac	4084	0,003	6345	0,036
Efalizumab	604	0,003	1374	0,006	Ezetimibe	800	0,005	1750	0,008
Etanercept	80	0,000	154	0,006	Fenofibrate	365	0,014	439	0,075
Famciclovir	210	0,014	660	0,032	Flutamide	300	0,100	303	0,158
Lansoprazol	978	0,004	2677	0,004	Fluvastatin	1048	0,003	1058	0,011
Losartán	762	0,010	751	0,011	Ibuprofen	4084	0,003	3516	0,004
Mesalamine	173	0,012	451	0,011	IFN beta 1a	187	0,043	373	0,236
Nimodipine	479	0,015	823	0,005	Infliximab	362	0,030	1304	0,040
Nizatidine	1729	0,010	2694	0,010	Leflunomide	128	0,023	190	0,042
Olmesartan	548	0,002	2145	0,002	Lisinopril	207	0,000	1349	0,001
Omeprazol	120	0,008	2631	0,010	Lovastatin	5512	0,003	10573	0,007
Oseltamivir	2404	0,010	2514	0,010	Meloxicam	4084	0,003	10048	0,002
Oxycodone	45	0,000	452	0,011	Moexipril	226	0,013	674	0,010
Pantoprazole	82	0,012	682	0,012	Montelukast	1180	0,012	1955	0,016
Paroxetine	2382	0,010	3268	0,010	Naproxen	4084	0,003	6249	0,004
Pergolide	187	0,011	189	0,011	Nevirapine	1128	0,044	1121	0,053
Rabeprazole	1456	0,002	237	0,008	Nifedipine	126	0,008	370	0,011
Repaglinide	108	0,010	1580	0,010	Olanzapine	115	0,000	243	0,025
Risperidone	424	0,009	448	0,010	Pegvisomant	32	0,031	80	0,063
Ropinirol	298	0,007	1423	0,006	Perindopril	223	0,009	789	0,016
Topiramate	204	0,005	514	0,014	Pioglitazone	793	0,003	1526	0,003
Triazolam	361	0,045	380	0,053	Pravastatin	13009	0,013	13010	0,014
Valaciclovir	768	0,008	2696	0,016	Rofecoxib	4084	0,003	7349	0,018
Valsartan	888	0,010	2316	0,010	Rosiglitazone	1000	0,002	1000	0,002
					Simvastatina	2430	0,014	2635	0,019
					Ticlopidine	508	0,016	525	0,044
					Tizanidine	261	0,010	264	0,030
					Valdecoxib	4084	0,003	2555	0,000
					Zafirlukast	2032	0,011	4058	0,015
					Zidovudine	428	0,026	453	0,031
					Zileuton	491	0,002	475	0,019

N_c = number of patients in clinical trials treated with placebo; I_c = incidence of incidence of ALT elevations $\geq 3 \times \text{ULN}$ in patients treated with placebo. N_D = number of patients in clinical trials treated with drug; I_D = incidence of ALT elevations $\geq 3 \times \text{ULN}$ in patients treated with drug.

REFERENCES

1. Lee W. Drug-induced hepatotoxicity. *N Engl J Med* 2003; 349: 474-85.
2. Kaplowitz N. Drug-induced liver disorders: implications for drug development and regulation. *Drug Saf* 2001; 24: 483-90.
3. Olson H, Betton G, Robinson D et al. Concordance of the toxicity of pharmaceuticals in humans and in animals. *Regul Toxicol Pharmacol* 2000; 32: 56-67.
4. Agency EM, CPMP. ICH Topic E 1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety; 1995.
5. Rosenzweig P, Miget N, Brohier S. Transaminase elevation on placebo during phase I trials: prevalence and significance. *Br J Clin Pharmacol* 1999; 48: 19-23.
6. Zimmerman H. *Hepatotoxicity: The Adverse Effects of Drugs and other Chemicals on the Liver*. 2 ed. Philadelphia: Lippincott Williams & Wilkins; 1999.
7. Gupta NK, Lewis JH. Review article: the use of potentially hepatotoxic drugs in patients with liver disease. *Aliment Pharmacol Ther* 2008; 28: 1021-41.
8. Moses P, Schroeder B, Alkhatib O, Ferrentino N, Suppan T, Lidofsky S. Severe hepatotoxicity associated with bromfenac sodium. *Am J Gastroenterol* 1999; 94:1393-6.
9. Watkins P. Insight into hepatotoxicity: The troglitazone experience. *Hepatology* 2005; 41: 229-30.
10. Clark J, Zimmerman H, Tanner L. Labetalol hepatotoxicity. *Ann Intern Med* 1990; 113: 210-3.
11. Chang CY, Schiano TD. Review article: drug hepatotoxicity. *Aliment Pharmacol Ther* 2007; 25: 1135–51.
12. Loke Y, Price D, Derry S, Aronson J. Case reports of suspected adverse drug reactions--systematic literature survey of follow-up. *BMJ* 2006; 332: 335-9.
13. Aronson J. Unity from diversity: the evidential use of anecdotal reports of adverse drug reactions and interactions. *J Eval Clin Pract* 2005; 11: 195-208.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
14. Arnaiz JA, Carné X, Riba N et al. The use of evidence in pharmacovigilance: case reports as the reference source for drug withdrawals. *Eur J Clin Pharmacol* 2001;57(1):89-91.
15. Willy M, Li Z. What is prescription labeling communicating to doctors about hepatotoxic drugs? A study of FDA approved product labeling. *Pharmacoepidemiol Drug Saf* 2004; 13: 201-6.
16. Zapater P, Such J, Pérez-Mateo M, Horga J. A new Poisson and Bayesian-based method to assign risk and causality in patients with suspected hepatic adverse drug reactions: a report of two new cases of ticlopidine-induced hepatotoxicity. *Drug Saf* 2002; 25: 735-50.
17. Watkins PB, Seligman PJ, Pears JS, Avigan MI, Senior JR. Using Controlled Clinical Trials to learn more about acute Drug-Induced Liver Injury. *Hepatology* 2008; 48: 1680-9.
18. Senior JR. Monitoring for hepatotoxicity: what is the predictive value of liver "function" tests?. *Clin Pharmacol Ther* 2009; 85: 331-4.
19. Kaplowitz N. Drug-induced liver disorders: introduction and overview. Kaplowitz N and DeLeve LD ed. *Drug-induced liver disease*. New York: Marcel Dekker, 2003: 1-13.
20. García-Cortés M, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ; Spanish Group for the study of Drug-induced Liver Disease (grupo de Estudio para las Hepatopatías Asociadas a Medicamentos, Geham). Evaluation of Naranjo Adverse Drug Reactions Probability Scale in causality assessment of drug-induced liver injury. *Aliment Pharmacol Ther* 2008; 27: 780-9.

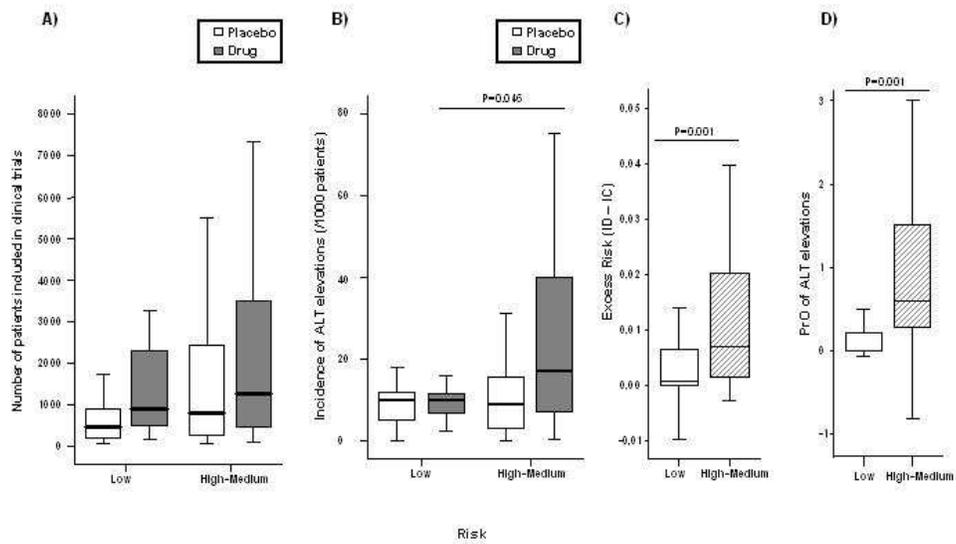
Figures

Figure 1 – Number of patients, incidence of ALT elevations, Excess Risk and Odds Ratio (PrO) detected in clinical trials with hepatotoxic drugs according to low or high-medium risk of hepatotoxicity. ID = drug incidence of ALT elevations. IC = placebo incidence of ALT elevations. Excess Risk = $I_D - I_C$. PrO = $(K_d - K_c) / K_c$, where K_d and K_c are the maximum number of occurrences of ALT $\geq 3 \times \text{ULN}$ in a population of drug or placebo-treated patients, respectively.

Figure 2 – A) Differences in the number of hepatotoxic drugs with a significant increase in incidence of ALT elevations in placebo-controlled clinical trials according to low or high-medium risk of hepatotoxicity. No significant or significant results were dichotomized according to Chi square test p value \geq or $<$ 0.05 B) Differences between low or high-medium risk of hepatotoxicity in the number of drugs with a relevant increase in Excess Risk of incidence of ALT elevations. C) Differences between low or high-medium risk of hepatotoxicity in the number of drugs with a relevant increase in Odds Ratio (PrO) of incidence of ALT elevations. Excess Risk ($I_D - I_C$) and PrO were dichotomized in no relevant or relevant result according to value \leq or $>$ upper quartile (75th percentile) calculated in the low risk group of drugs.

Figure 3 - Number of Hepatotoxicity published case-reports according to drug risk (A), Chi square test result (B), differences in Excess Risk ($I_D - I_C$) (C) and differences in Odds Ratio (PrO) (D). Number of published case reports and rate of case reports published by year were categorized in three groups: \leq 25th percentile (≤ 1), between 25th and 75th percentiles (1-9) and $>75^{\text{th}}$ percentile (>9).

Figure 1

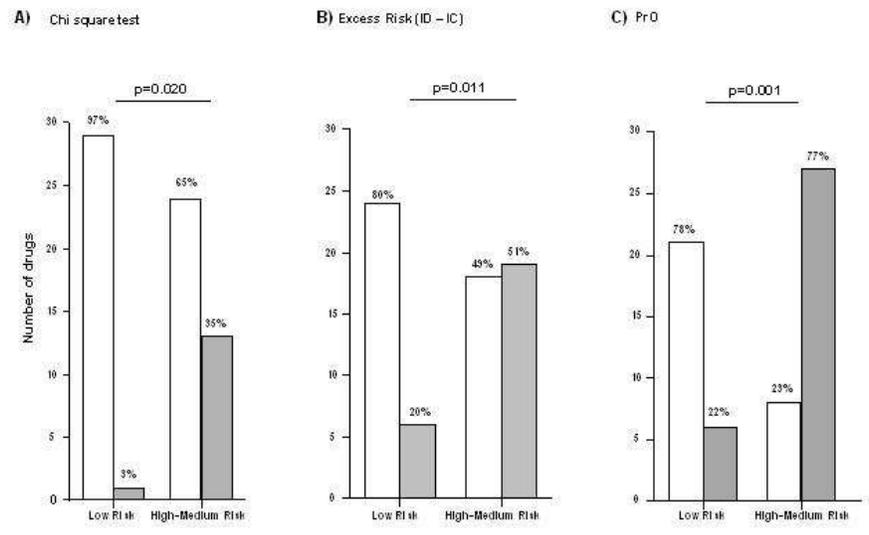


254x190mm (72 x 72 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 2

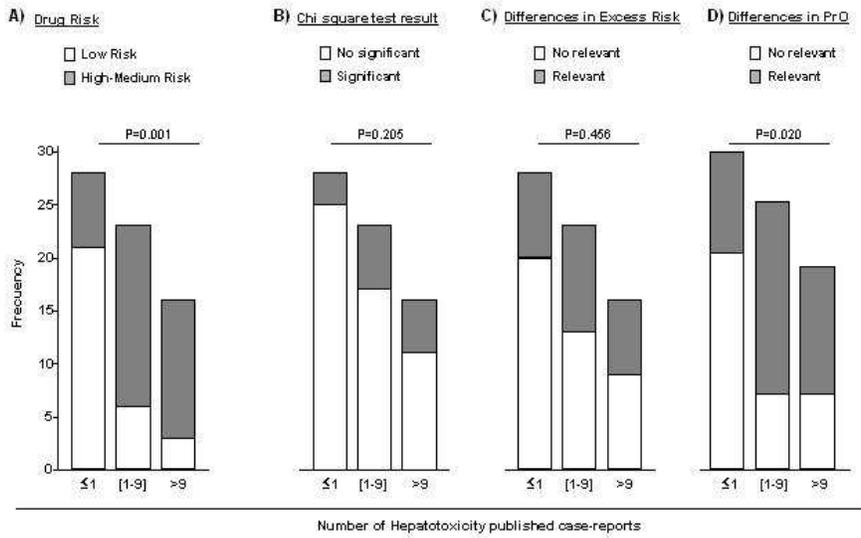
□ No Significant difference
■ Significant difference



254x190mm (72 x 72 DPI)

Review

Figure 3



254x190mm (72 x 72 DPI)

Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60