



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

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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.

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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 clasified 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

reports have been identified as the most important source of information that finally may lead to withdraw a drug from the market for safety reasons¹⁴.

DILI profile in most drugs' available information is based on both the incidence of elevations of ALT in clinical trials and published case reports. To the best of our knowledge, the relationship between these two sources of information has not been studied. The aim of this investigation has been to assess the value of ALT elevations in clinical trials as predictors of the development of hepatotoxicity, expressed as the number of published case reports in the postmarketing setting.

Methods

Identification of drugs showing elevations of ALT 3 times above ULN (ALT ≥3xULN) in clinical trials: we used the search tool available in 2007 Physicians' Desk Reference (PDR 2007) to identify potentially hepatotoxic drugs. For the purpose of this study, a 'hepatotoxic drug' was defined as a prescription drug for which the terms [(hepatic enzymes elevated) OR (hepatotoxicity) OR (elevated aminotransferases) OR (liver injury) OR (hepatic dysfunction) OR (increased SGPT) OR (liver damage) OR (elevated ALT) OR (elevated serum transaminases) OR (liver test abnormalities) OR (hepatic/liver failure) OR (hepatic/liver necrosis)] were explicitly stated in product labelling. Drugs indicated for the treatment of hepatitis B or C, antineoplastic agents, products containing more than one active ingredient, hormones, vitamins, blood derivatives and topical drugs were excluded.

Information on the incidence of elevations of ALT (≥3xULN) for drug-treated and placebo-treated patients (I_D and I_C, respectively) was retrieved either from product labelling, Food and Drug Administration (FDA) or European Medicines Agency (EMA) assessment or review reports. A Pubmed search was also performed to look for placebo controlled clinical trials or meta-analysis, using the limits "All Adult: 19+ years, Comparative Study, Humans". When no information about the number of drug-treated and placebo-treated patients with ALT

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$\geq 3 \times \text{ULN}$ was available but the product labelling made an unspecific asseveration like " $\text{incidence} \leq 0.01$ ", this maximal incidence was recorded and the number of patients with ALT $\geq 3 \times \text{ULN}$ 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 $\geq 3 \times \text{ULN}$ 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 $\text{PrO} = (K_D - K_C) / K_C$, where K_D and K_C are the maximum number of occurrences of ALT $\geq 3 \times \text{ULN}$ episodes that could be detected with a probability of 0.05 or higher in a population of drug or placebo-

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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.
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12 Chi square test results were dichotomized in non significant or significant
13 according to p value \geq or $<$ 0.05. Excess Risk ($I_D - I_C$) and PrO were
14 dichotomized in no relevant or relevant result according to value \leq or $>$ upper
15 quartile (75th percentile) calculated in the low risk group of drugs.
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20 Number of published case reports and rate of case reports published by year
21 were categorized in three groups: $<$ 25th percentile, between 25th and 75th
22 percentiles and $>$ 75th percentile.
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27 Quantitative data are described as median and interquartile range (IQR).
28 Qualitative data are described as frequencies or percentages with 95%
29 confidence intervals calculated using the binomial distribution. Differences
30 between groups were analyzed through the U-Mann-Whitney non-parametrical
31 test for quantitative variables and the Chi-square test for qualitative ones. A
32 difference was considered significant if $p < 0.05$. All statistical analysis was
33 performed using SPSS 14.0 software.
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42 **Results**
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45 A total of 204 potentially hepatotoxic active substances were retrieved. Thirty-
46 eight of them were excluded because the product information indicated only the
47 need for dose adjusting in hepatic insufficiency. Five were excluded due to their
48 indication for therapy of patients with chronic hepatitis B or C virus infection. A
49 hundred and sixty one drugs were finally selected, but sufficient information to
50 calculate the incidence of ALT elevations $\geq 3 \times \text{ULN}$ in treatment and placebo
51 groups was available only for 67 active substances (42%). Four of them
52 (pergolide, efalizumab, rofecoxib and valdecoxib) had been withdrawn from the
53 market due to safety reasons other than hepatotoxicity by the time this study was
54 performed. Table 1 show a list of these drugs, the number of drug-treated and
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placebo-treated patients (N_D and N_C , respectively) and their corresponding incidences (I_C and I_D , respectively).

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

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

A higher incidence of ALT elevations $\geq 3 \times \text{ULN}$ was observed for patients treated with high-medium risk drugs (median 17/1000; IQR 7-40/1000) compared to patients treated with low risk drugs (median 10/1000; IQR 7-12/1000; Figure 1. B; $p=0.046$). This significant difference in I_D was also observed when $I_D - I_C$ and PrO were calculated (Figures 1.B y 1.C). Patients treated with high-medium risk drugs showed an increase of risk of 7/1000 (IQR 1-20/1000) with respect to placebo treated patients, being significantly higher than the increase shown by patients in the low risk drugs (1/1000; IQR: 0-6 /1000; $p=0.001$). Median PrO value for patients treated with high-medium risk drugs (0.6; IQR 0.26-1.61, equivalent to a probability of 37.5%; IQR 20.6-61.7%) was significantly higher compared with patients treated with low risk drugs (0.0; IQR: 0.0-0.25, equivalent to a probability of 0%; IQR 0.0-20.0%; $p = 0.001$).

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

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

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

Time “at risk” and number of case-reports

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

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

Relationship between clinical trials data and case reports

No significant differences were observed in the number of published cases between drugs that had shown a significant difference in the incidence of ALT as compared to those drugs which had not (Figure 3.B). Similarly, no relevant differences were observed in the number of published cases for drugs with a higher excess risk compared to drugs with a lower excess risk (Figure 3.C). However, those drugs with a relevant difference according to the PrO value

were significantly associated with a higher number of published case reports (Figure 3.D; $p=0.020$).

Discussion

In this investigation we show evidences of a relationship between drug-induced serum ALT elevations in premarketing studies and the number of DILI case-reports published in the postmarketing setting.

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

Indeed, we have observed that the labelling of approximately 60% of the drugs here evaluated that are considered as potentially hepatotoxic does not include information regarding the frequency of ALT elevations in premarketing clinical trials, suggesting that analytical and clinical evidences other than ALT elevations were considered in the drug labelling procedure.

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

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

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

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

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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.

None of the authors of this article have any conflicts of interest to declare.

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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.

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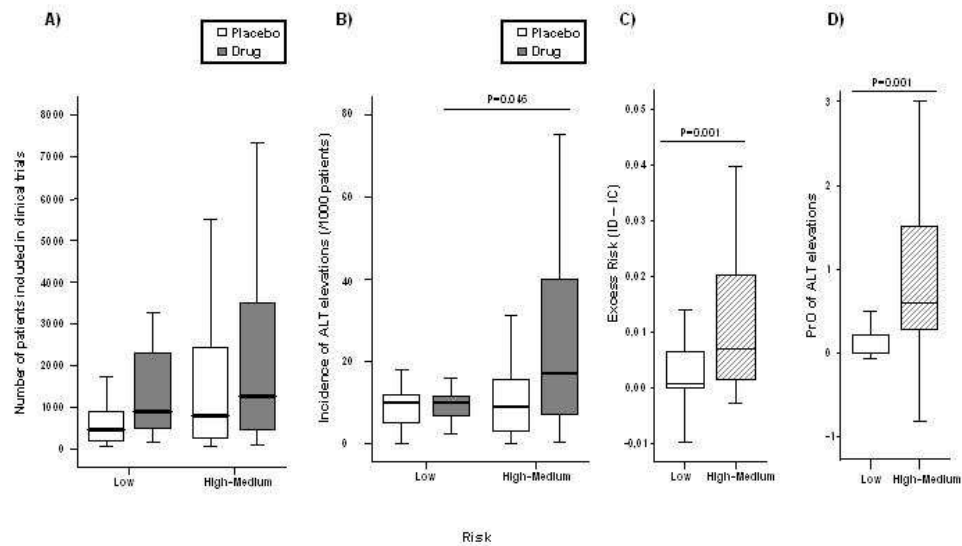
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Figures

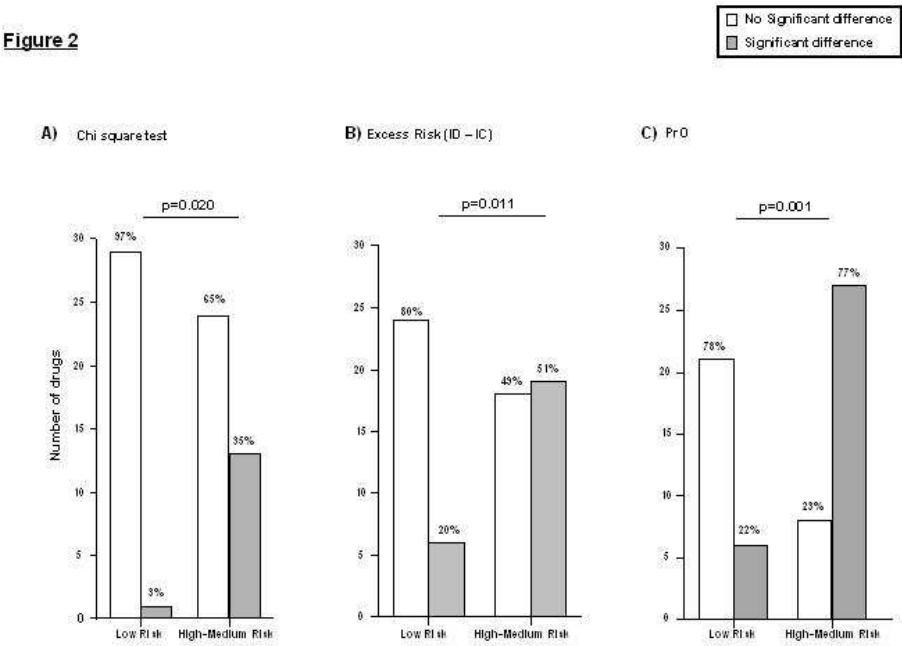
Figure 1 – Number of patients, incidence of ALT elevations, Excess Risk and Odds Ratio (PrO) detected in clinical trials with hepatotoxic drugs according to low or high-medium risk of hepatotoxicity. ID = drug incidence of ALT elevations. IC = placebo incidence of ALT elevations. Excess Risk = $I_D - I_C$. 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).

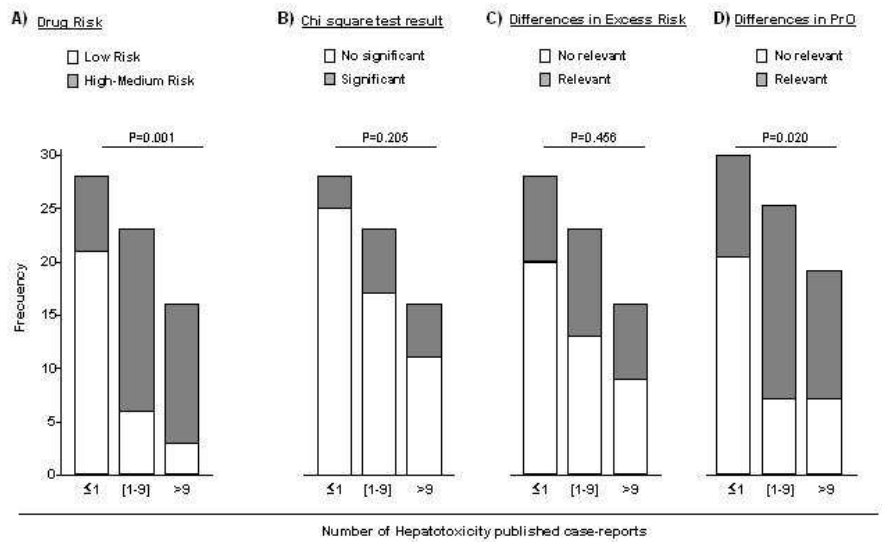
Figure 1

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Figure 3



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