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Risk of Hepatic Events in Patients Treated with Vancomycin in Clinical Studies

A Systematic Review and Meta-Analysis

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Abstract

Background: Routine surveillance of spontaneous reporting data and subsequent disproportionality analyses have indicated that the use of vancomycin might be associated with an increased risk of hepatic events.

Objective: To conduct a meta-analysis of published randomized controlled clinical trials (RCTs) to better understand if the use of vancomycin is potentially associated with an increased risk of hepatic events.

Data Sources: A comprehensive search and review of published clinical studies indexed in MEDLINE, PubMed, International Pharmaceutical Abstracts and the Cochrane Library from 1950 to June 2010 was conducted.

Study Selection: The inclusion criteria consisted of (i) published RCTs comparing vancomycin with/without other additional treatments to other comparators; and (ii) studies that reported hepatic events.

Data Extraction: The data related to any hepatic events reported in RCTs were extracted and examined. The quality of selected studies was assessed based on the Jadad scale. The effect size was presented as a risk ratio (RR) with a 95% CI and number needed to harm. The pooled RRs were calculated by using both fixed-effects and random-effects models. The impact of publication bias was assessed by funnel plot and the Egger's test.

Data Synthesis: A total of 20 RCTs, including 7419 patients, met the study inclusion criteria and were selected. An increased incidence of hepatic events, specifically elevated serum aminotransferase levels, was observed in patients receiving vancomycin, when compared with other comparators (pooled RR = 1.95; 95% CI 1.62, 2.36; $p < 0.001$), but the majority of the events were mild to moderate in nature. No evidence is currently available suggesting that the use of vancomcycin confers a risk of progressive or severe drug-induced liver injury.

Conclusions: Continuous monitoring of hepatic events on a routine basis among patients with the use of vancomycin is suggested.

Background

More than half a century ago, an organic chemist at Eli Lilly and Company, Dr E.C. Kornfield, isolated a compound from a sample of soil collected in Borneo.[1] The compound, now known as vancomycin, had a high degree of bactericidal activity against most Gram-positive organisms, including penicillin-resistant staphylococci.[2] In 1956, after receiving approval from the US FDA, vancomycin was introduced in the US as a possible treatment for infections due to penicillin-resistant *Staphylococcus aureus*. However, vancomycin was not widely used, due to the subsequent discovery of methicillin and other anti-staphylococcal penicillins, until the beginning of the early 1980s when worldwide methicillin-resistant staphylococci emerged.

Overall, vancomycin is considered to have a favourable safety profile in clinical use. In the early trials of vancomycin, although auditory toxicity and nephrotoxicity were reported, it is likely that these problems partially occurred as a result of the presence of impurities in the earlier preparations of vancomycin.[3] Other toxicities, such as rash, chills and venous irritation, were reported but considered to be infusion related.[4] Hepatic toxicity has not been associated with the administration of either oral or intravenous vancomycin.[5] However, during a recent routine safety review conducted internally by Eli Lilly, based on spontaneous reporting data collected from July 2007 to June 2008, 14 cases of hepatic enzyme and/or bilirubin elevations in association with vancomycin use were encountered. Most of the cases (71.4%) were deemed to be drug related, but non-serious (86.0%) and reversible. Sixty-four percent of cases were reported with elevation of ALT and AST up to 5×the upper limit of normal (ULN). The disproportionality analyses, including proportional reporting ratio and empirical Bayes geometric mean,[6,7] using FDA spontaneous reporting data also indicated disproportionally increased reporting of abnormal liver function tests (ALFTs) with the use of vancomycin. In 2006, a first case of vancomycin-induced elevation of hepatic enzyme levels was reported,[8] when a 57-year-old man was treated with oral vancomycin on five separate occasions (dosages from 125 to 500 mg/day), each of which led to significant elevations in ALT (to 371 U/L). Interpretation of spontaneous case reports is difficult since many patients requiring vancomycin treatment are likely to exhibit elevated aminotransferases and bilirubin levels because of their infectious processes.[9]

Given the known limitations associated with spontaneous reports and the potentially serious consequences of hepatic events, a systematic review of published randomized controlled clinical trials (RCTs) and meta-analysis was undertaken to assess whether the use of vancomycin was associated with an increased risk of hepatic events when compared with other antibacterial agents.

Methods

Inclusion Criteria and Literature Search

For this systematic review and meta-analysis, inclusion criteria consisted of (i) RCTs comparing vancomycin monotherapy and/or in combination with other treatments to other comparators; and (ii) RCTs with available information with respect to the number of patients experiencing hepatic events at the end of treatment.

A search of materials published in English was conducted by two reviewers (YC, MZ) using MEDLINE (1950–June 2010), PubMed (1950–June 2010), CINAHL (1982–June 2010), International Pharmaceutical Abstracts (1970–June 2010) and the Cochrane Library (1960–June 2010). Information published in Chinese was identified by two reviewers (YC, XYY) using the Chinese National Knowledge Infrastructure (1979–June 2010). Keyword Boolean search was used to identify possible articles. The keywords used in the search were 'vancomycin', 'clinical trial', 'therapeutic use', 'hepatocellular injury', 'drug-induced liver injury (DILI)', 'hepatotoxicity', 'hepatic dysfunction', 'liver enzyme' and 'treatment outcome'. Articles of interest that were listed in the references of all retrieved articles were identified manually and reviewed. The reviewers for the English literature and those for the Chinese literature independently reviewed studies for inclusion. Any disagreements on inclusion were resolved through discussion.

Data Extraction

For the included studies, data were extracted by two reviewers (YC, MZ) independently. Any disagreements on data extraction and study evaluation were resolved through discussion. Data relating to any hepatic events reported in RCTs were extracted and examined, including elevated serum aminotransferase levels (i.e. ALT and/or AST), abnormal serum total bilirubin (TBL) and ALFTs. In addition, data were collected regarding the characteristics of patients, characteristics of studies, treatment indications, other concomitant medication use and treatment duration.

The quality of each included study was evaluated using the Jadad scale[10] on the basis of information with respect to randomization, blinding and reporting of withdrawal and/or dropouts. One point is assigned for each 'yes' and a 0 point is given for each 'no'. One additional point is given when detailed descriptions of the methods of randomization and/or double-blinding are presented.

Data Synthesis

The endpoint of this meta-analysis was the incidence of hepatic events. The incidence was calculated by dividing the number of patients who received treatment and experienced any hepatic events at the end of study by the total number of patients who received the treatments. The risk of hepatic events across different treatment groups was measured as the risk ratio (RR) and number needed to harm (NNH).[11] The RR is defined as the ratio of the incidence of hepatic events among patients receiving vancomycin monotherapy and/or in combination with other treatments to the incidence among patients receiving other treatments except vancomycin. The computation of RR and the 95% CI were conducted using the following formula (equation 1):

$RR = (a_i / n_{1i})/(c_i / n_{2i})$ with the standard error (SE) of the log RR

$$SE\{Ln(RR)\} = \sqrt{1/a_i + 1/c_i - 1/n_{1i} - 1/n_{2i}} \quad \text{(Eq. 1)}$$

where a_i and c_i are the events, n_{1i} and n_{2i} are the group size, for intervention and control group in the study i, respectively.

The NNH is defined as the inverse of the difference in incidence between patients receiving vancomycin monotherapy and/or in combination with other treatments and patients receiving other treatments except vancomycin.

In this study, RevMan 4.27 (Cochrane Collaboration, Oxford, UK) was used for data analysis.[12] The significance level was predetermined at a level of 0.05. The pooled RRs were calculated by using both fixed- and random-effects models.[13] If the test of heterogeneity (χ^2 statistic) was significant ($p < 0.05$), the results of the random-effects model were presented; otherwise, estimated results based on the fixed-effects models were presented. Since most studies reported hepatic events as elevated serum aminotransferase levels, in addition to analysis of hepatic events in general, subgroup analyses were performed by only including studies where the hepatic events were specifically reported as elevated serum aminotransferase levels. Additional analyses were conducted by including the studies where vancomycin monotherapy was evaluated. The robustness of the pooled estimates was assessed by repeating the meta-analysis based upon the quality of studies, which was determined by the sample size (e.g. n >150) and the adequate information with respect to blinding (e.g. double-blinding).

Given the consideration that studies with positive findings are generally more likely to be published compared with studies with negative findings, publication bias was assessed using the funnel plot regression method.[14] When there is no publication bias, the regression intercept has a predicted value of 0, forming a regression line that runs through the origin.

Results

Identified Studies and Characteristics

The initial literature search identified 395 articles. Of these, 45 articles were initially identified and reviewed and other studies were excluded due to either lack of adequate randomization or

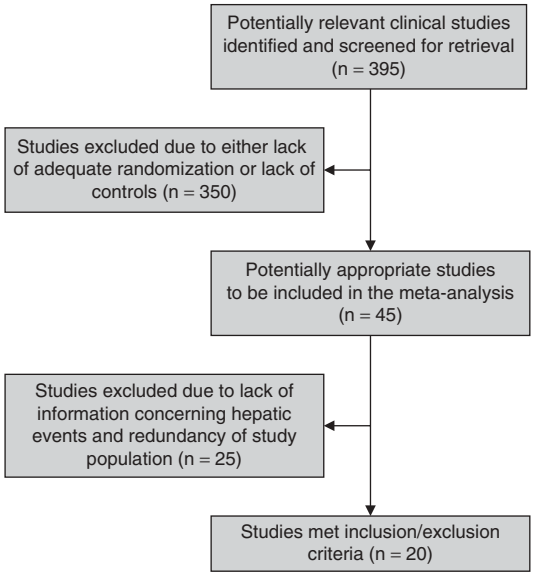

Fig. 1. Flowchart of the literature reviewing process.

lack of controls. Of the 45 studies, 24 further studies, including four meta-analyses, were then also excluded since no information was provided concerning hepatic events. One study was excluded since the study population described in that article is a subset of the study population reported in another study. The remaining 20 studies[15-34] met the inclusion criteria and were included into this study (figure 1), which included a total of 7419 patients with infectious diseases (table I).

In the 20 identified studies, vancomycin was administered intravenously, except in the study of Wilson et al.[17] study where the route of treatment was unknown. There were nine studies where vancomycin monotherapy was evaluated[17,20,24-26,29,31,32,34] and the remaining studies included vancomycin in combination with other antibacterials. In the comparison groups, the antibacterial comparators included linezolid, telavancin tigecycline, teicoplanin, ticarcillin/clavulanic acid combination, cephalosporin, ticarcillin, amikacin, ceftazidime, aztreonam and daptomycin. Of the 20 studies, complicated skin and skin structure infection (cSSSI) was the treatment indication for 11 studies, and the other indications included nosocomial pneumonia, febrile neutropenia and sepsis (table I).

The definitions of reported hepatic events varied across the studies (table I). Two studies reported the occurrence of hepatotoxicity in general.[29,33] One study reported the hepatic events as hepatic dysfunction.[17] In the remaining studies, the hepatic events were reported as either elevated levels of ALT/AST or ALFTs in general. One study[20] reported that 3.7% of patients receiving vancomycin had ALT elevation to ≥3 × the ULN; however, this was not significantly different from the comparator group (2.3%). Another three studies reported substantially abnormal ALT and TBL values,[25-27] in which the substantially abnormal values were defined as more than 2 × the ULN or 2 × the baseline if the baseline was abnormal. Overall, the majority of the reported hepatic events were mild to moderate increases in ALT and AST levels.

Most studies appeared to have an appropriate randomization sequence. Nine studies were double-blinded and the others were either open-label or single-blinded studies (table I). Among 15 studies with reported dropout/withdrawal, the rates ranged from 3.7%[18] to 66.1%.[15] According to the Jadad scoring method,[10] one study scored 4 points,[20] 9 scored 3 points,[15,16,18,19,21,22,24,30,31] and the rest of the studies scored 2 points.

The Risk of Hepatic Events in Association with Vancomycin

Regimens Containing Vancomycin versus Other Regimens

The estimated incidence of hepatic events in general in the group of patients receiving vancomycin with or without other treatments was 6.8%, when compared with 3.9% among patients receiving other regimens without vancomycin (pooled RR 1.83; 95% CI 1.54, 2.17; $p < 0.001$) [figure 2]. The NNH is 35, indicating that one of 35 patients might develop a hepatic event if exposed to vancomycin.

Based on the studies where the hepatic events were specifically reported as elevated serum aminotransferase levels,[15,16,18-20,22,25-28,31] the estimated incidence of elevated ALT and/or AST in vancomycin and non-vancomycin groups was 7.8% and 4.2%, respectively (pooled RR 1.95; 95% CI 1.62, 2.36; $p < 0.001$).

Table I. Characteristics of selected randomized controlled trials (RCTs) and patients

Study (y)	Blinding	Vancomycin regimen	Non-vancomycin regimen	Indication	Measurement of hepatic events	Vancomycin group/non-vancomycin group			Duration (mean [days])	No. of dropouts or withdrawals/ total no. of patients	ITT
						no. of patients	sex (male [%])	age (mean [y])			
Shenep et al.[15] (1988)	DB	V + T + A	P + T/C + A	FN in Paeds	2× ↑ in AST or ALT, TBL	53/48[a]	52.8/58.3	7.1/8.1	10/8[a]	197/298	NR
Calandra et al.[16] (1991)	NR	V + C + A	C + A	FN	2× ↑ in AST or ALT	383/370[a]	62.0/66.0	37.0/39.0	≥7	138/891	NR
Wilson et al.[17] (1994)	NR	V	TEI	Various	Hepatic dysfunction	239/238	NR	NR	NR	NR	NR
Breedt et al.[18] (2005)	DB	V + AZ	TIGI	cSSSI	ALT ↑ AST ↑	269/274	60.6/60.9	50.1/48.8	NR	20/543	Yes
Sacchidanand et al.[19] (2005)	DB	V + AZ	TIGI	cSSSI	ALT ↑ AST ↑	281/292	66.9/61.6	48.4/49.4	NR	37/573	Yes
Stryjewski et al.[20] (2008)	DB	V	TELE	cSSSI	ALT >3× ULN AST >3× ULN	939/928	60/56	48.7/48.8	10/9	174/1867	NR
Stryjewski et al.[21] (2006)	DB	V (93%) or BL (7%)	TELE	cSSSI	↑ LFTs (ALT, AST)	95/100	65/55	42.3/44.7	NR	13/195	NR
Stryjewski et al.[22] (2005)	DB	V or BL	TELE	cSSSI	ABN AST and/or ALT	83/84	55/64	44.3/44.6	7/7[b]	9/167	NR
Arbeit et al.[23] (2004)	SB	V (172)/ PRP (284)	DAP	cSSSI	ABN LFT	558/534	55/55	51.9/51.5	NR	48/1092	Yes
Lin et al.[24] (2008)	DB	V	LIN	cSSSI	Mild ABN LFT	71/71	59.2/64.8	59.6/56.3	10.7/12.2	24/142	Yes
Jantausch et al.[25] (2003)	OL	V	LIN	Bacteraemia/ NP Paeds	S ABN ALT, TBL	48/104	60.4/55.8	2.65/2.61	12.8/10.5	NR	Yes
Deville et al.[26] (2003)	OL	V	LIN	GPI neonates	S ABN ALT, TBL	20/43	60.0/55.8	40.3/25.7[c]	10.3/11.5	14/63	Yes
Kaplan et al.[27] (2003)	OL	V and oral therapy	LIN	R GPI Paeds	S ABN ALT, TBL	101/215	58.4/54.4	2.94/2.19	12.2/11.3	77/316	Yes
Talbot et al.[28] (2007)	SB	V (PRP as appropriate) + AZ	Ceftaroline	cSSSI	↑ ALT	33/67	59.4/55.2	44/41.6	8.0/7.8	3/100	NR
Vazquez et al.[29] (1999)	NR	V	TEI	FN (second-line)	Hepatotoxicity (undef.)	38/38	55/39	47/51	NR	7/76	NR
Rubinstein et al.[30] (2001)	DB	V and AZ	LIN and AZ	NP	ABN LFT	193/203	67.8/70.0	61.3/62.8	8.9/9.6	112/396	Yes

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Table I. Contd

Study (y)	Blinding	Vancomycin regimen	Non-vancomycin regimen	Indication	Measurement of hepatic events	Vancomycin group/non-vancomycin			Duration (mean [days])	No. of dropouts or withdrawals/ total no. of patients	ITT
						no. of patients	sex (male [%])	age (mean [yr])			
Florescu et al.[31] (2008)	DB	V	TIGI	cSSSI	ALT ↑ AST ↑	39/117	59/65	51/51[b]	13.1/11.4	28/156	Yes
Lv et al.[32] (2004)	NR	V	Cephalosporin	NP neonates	ALT ↑ AST ↑	26/16	61.5/81.3	NR	NR	NR	NR
Neville et al.[33] (1995)	NR	V + others	TEI + others	GPI	Hepatotoxicity (undef.)	28/28	57.7/50.0	32/38[b]	8.5/10[a]	7/56	Yes
Kohno et al.[34] (2007)	OL	V	LIN	NP, cSSSI	ABN ALT	51/100	70.6/70.0	67.5/68.4	10.6/10.9	48/151	Yes

a No. of evaluable patients.

b Median rather than mean.

c Days.

A = amikacin; **ABN** = abnormal; **AZ** = aztreonam; **BL** = β-lactam; **C** = ceftazidime; **cSSSI** = complicated skin and skin structure infection; **DAP** = daptomycin; **DB** = double-blind; **FN** = febrile neutropenia; **GPI** = Gram-positive infections; **ITT** = intent-to-treat; **LFT(s)** = liver function test(s); **LIN** = linezolid; **NP** = nosocomial pneumonia; **NR** = not reported; **OL** = open label; **P** = placebo; **Paeds** = paediatric patients; **PRP** = penicillinase penicillin; **R** = resistant; **S** = substantially; **SB** = single-blind; **T** = ticarcillin; **TBL** = total bilirubin; **T/C** = ticarcillin/clavulanic acid; **TEI** = teicoplanin; **TELE** = televancin; **TIGI** = tigecycline; **ULN** = upper limit of normal; **undef.** = undefined; **V** = vancomycin; ↑ indicates increase.

On the basis of three studies with serum TBL values reported,[25-27] no significant difference was found in terms of abnormal TBL values between the vancomcyin and the non-vancomycin groups (pooled RR 0.74, 95% CI 0.37, 1.47; p = 0.39).

Vancomycin Monotherapy versus Other Monotherapy

In the RCTs where patients who received vancomycin monotherapy were evaluated and compared with patients receiving other monotherapy,[17,20,24-26,29,31,32,34] the estimated incidence of hepatic events in general was 4.3% in the vancomycin group, while the incidence was 2.6% in patients receiving other treatments (pooled RR 1.91; 95% CI 1.37, 2.66; p < 0.001) [figure 3].

Sensitivity Analyses and Assessment of Publication Bias

A significant difference in the incidence of hepatic events in general was also seen in the studies with larger sample sizes (pooled RR 1.75; 95% CI 1.41, 2.17; p < 0.001)[16-20,23,30] and the studies with double-blind design (pooled RR 2.35; 95% CI 1.82, 3.03; p < 0.001).[15,18-22,24,30,31]

Using the Egger's test[14] it was found that the predicted intercept of the regression was 0.48 (95% CI −0.65, 1.61), suggesting that the significantly increased reporting of hepatic events was less likely due to publication bias. The funnel plot of standard error by RR is shown in figure 4.

Discussion

Drug-induced liver injury (DILI) has been the most frequent cause of the withdrawal of medications from the market for the past 50 years.[35] In most cases, the overall occurrence of severe DILI is infrequent, affecting one in 10 000–100 000 persons.[36] However, mild elevations of serum aminotransferase levels, usually without any apparent symptoms, are often seen during drug development and post-approval periods. In this study, an excess of aminotransferase elevations compared with control groups was seen in patients receiving vancomycin. The observed rise of serum aminotransferase levels due to the release of ALT and AST from injured liver cells

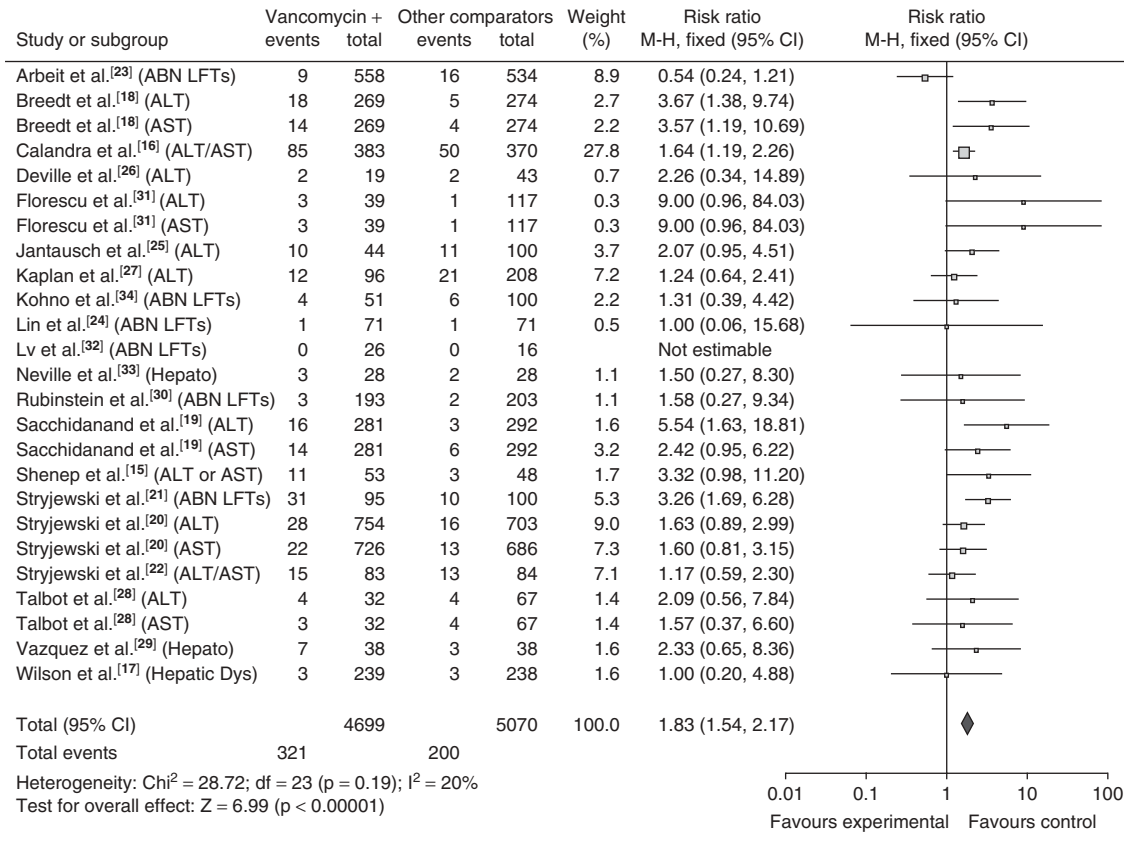

Fig. 2. The risk of hepatic events in patients with the treatment regimens containing vancomycin. **ABN** = abnormal; **df** = degrees of freedom; **Hepatic Dys** = hepatic dysfunction; **Hepato** = hepatotoxicity; **LFTs** = liver function tests; **M-H** = Mantel-Haenszel test.

indicates potential hepatocellular injury. In general, many drugs, including some commonly used antibacterials, could cause laboratory evidence of hepatocellular injury. It should be noted, however, that the ability to cause liver injury is not a specific predictor of a drug's potential for severe DILI.[35,37] In the 20 included studies, the majority of the reported hepatic events appear to be mild to moderate, which is consistent with the review of 14 spontaneous cases that led to this analysis. More importantly, no significant decrease of hepatic functional ability, reflected by the abnormal serum TBL levels, was reported in patients receiving vancomycin. In the three studies that reported abnormal TBL values, no statistically significant difference was found between the vancomycin and non-vancomycin groups ($p = 0.39$). In the single case report by Cadle and colleagues,[8] although patients experienced significant elevation of ALT and AST, abnormal serum TBL levels were not reported. Therefore, although the use of vancomycin may cause transient and mild rises in serum aminotransferase levels based on the included RCTs, no evidence currently exists suggesting that the use of vancomycin confers a risk of progressive or severe DILI.

It is believed that the mechanism of DILI often involves two pathways: direct hepatotoxicity and adverse immune reactions.[37] In most instances, DILI is initiated by the direct action of a drug or a reactive metabolite of a drug, which may cause injury to hepatocytes. Hepatocellular damage may trigger the activation of cells from the innate immune system, such as Kupffer cells and natural killer cells, which can initiate an inflammatory reaction and/or an adaptive immune response.[37-39]

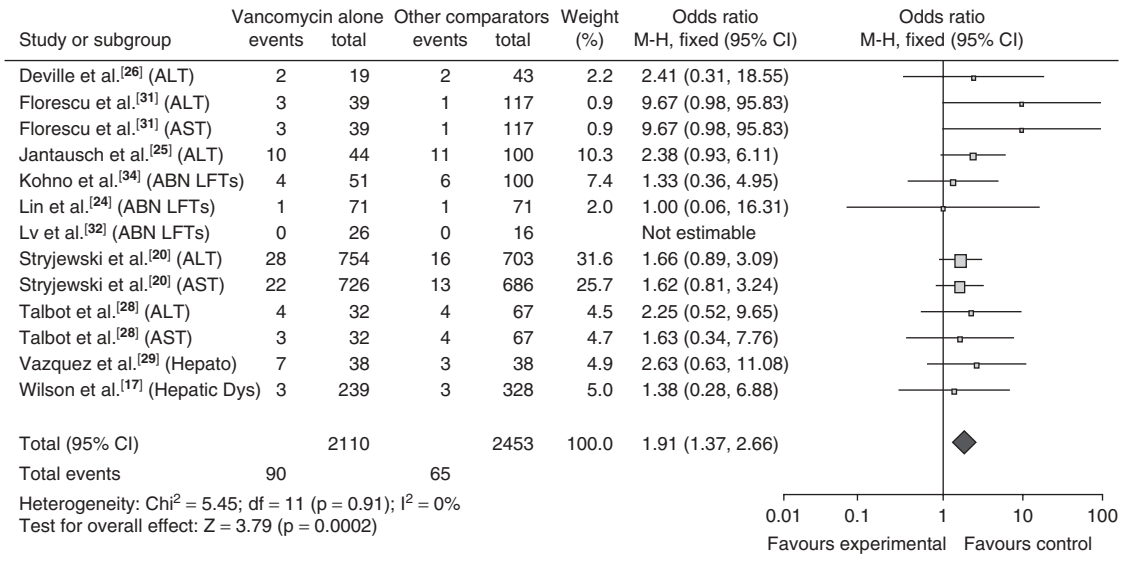

Fig. 3. The risk of hepatic events in patients treated with vancomycin monotherapy. **ABN** = abnormal; **df** = degrees of freedom; **Hepatic Dys** = hepatic dysfunction; **Hepato** = hepatotoxicity; **LFTs** = liver function tests; **M-H** = Mantel-Haenszel test.

The potential mechanism for the elevated serum aminotransferase associated with the use of vancomycin may be due to one of the two pathways, or both. Although this is, to our knowledge, the first study examining the risk of vancomycin-related hepatic events using clinical trial data, it is not the first to report abnormalities in liver enzyme and TBL values in patients with infectious diseases and bacteraemia.[9,40] The pathogenesis of hepatic injury during sepsis is believed to be multifactorial, including bacterial endotoxins, malnutrition, fever, haemolysis, decreased hepatic blood flow and metabolic abnormalities secondary to hypermetabolism during sepsis. Given the randomized and controlled nature of RCTs, the disease-related factors may be responsible, at least in part, for the elevated serum aminotransferase levels, but are less likely to account for the significant difference in the incidence of serum aminotransferase elevations between the vancomycin group and non-vancomycin groups.

The findings of this study should be interpreted within the context of the limitations. First, this systematic review with meta-analysis is, by nature, retrospective as the studies were identified after they had been completed. Although all the included studies are RCTs, they varied greatly with respect to study population, inclusion and exclusion criteria, treatment indication and particularly the definitions of reported hepatic events. Our study was unable to adjust for those differences before pulling together the studies, which might confound our observations and add difficulties to the interpretation of the findings. Second, since the primary endpoints of the included 20 studies are not exclusively focused on the liver safety of medications included, there is a significant lack of information on the diagnosis, progression and outcomes of hepatic events as well as detailed causality assessment. In addition, other alternative causes of hepatocellular injury were

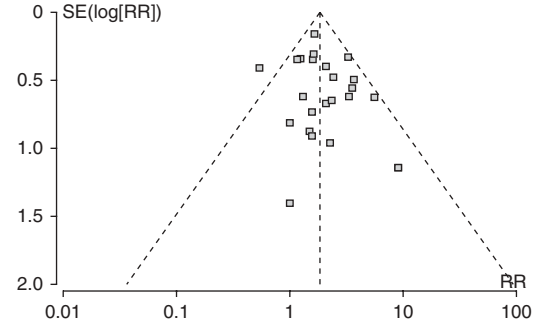

Fig. 4. Funnel plot of standard error by risk ratio (RR). **SE** = standard error.

not fully examined at baseline, such as viral, autoimmune or alcoholic hepatitis; gall bladder or biliary tract disorders; circulatory problems such as hypotension or heart diseases causing hypoxic hepatopathy; and concomitant use of a known hepatotoxic drug (e.g. aztreonam, ceftazidime) or exposure to hepatotoxins. Therefore, it is possible that the observed risk of hepatic events might be due to some pre-existing conditions rather than vancomycin treatment. Third, observation built upon RCTs often suffers from insufficient sample size. In our study, only 8 of 20 studies included more than 100 patients in each treatment group, which might have reduced the ability of this study to assess the risk of some rare but serious adverse events, such as severe DILI. According to the rule of three, given the incidence of severe DILI of one per 10 000 persons, 30 000 people will be needed in order to have at least a 95% chance of seeing one or more cases of severe DILI.[41] Therefore, the absence of severe DILI in the identified studies may be due to the fact that those studies are not powered adequately to detect such a rare event. Fourth, due to the limited number of studies that involved newborn children and oral vancomycin, our study was unable to differentiate the risk of hepatic events between newborn and adults, and between oral and intravenous administration of vancomycin. Other limitations included the restriction of literature review to articles written in either English or Chinese, which limits the generalizability of the findings, and the lack of information on the manufacturer and the source of vancomycin, which does not allow the study to tease out the effects of impurity on the risk of liver enzyme elevation.

Conclusions

Despite the limitations, this is the first study to examine the risk of hepatic events associated with the use of vancomcyin based on a meta-analysis of clinical trial data, which helps clarify the potential safety signal originated from routine pharmacovigilance. The occurrence of hepatic events, specifically elevated serum aminotransferase levels, is more frequently reported in patients receiving vancomycin compared with other treatments included in this study, but the majority of events are mild to moderate in nature. Although no evidence currently suggests that the use of vancomcycin confers a risk of progressive or severe DILI, continuous monitoring of hepatic events on a routine basis among patients with the use of vancomycin is suggested.

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