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ORIGINAL ARTICLE

Herbalife hepatotoxicity: Evaluation of cases with positive reexposure tests

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Abstract

AIM: To analyze the validity of applied test criteria and causality assessment methods in assumed Herbalife hepatotoxicity with positive reexposure tests.

METHODS: We searched the Medline database for suspected cases of Herbalife hepatotoxicity and retrieved 53 cases including eight cases with a positive unintentional reexposure and a high causality level for Herbalife. First, analysis of these eight cases focused on the data quality of the positive reexposure cases, requiring a baseline value of alanine aminotransferase (ALT) < 5 upper limit of normal (N) before reexposure, with N as the upper limit of normal, and a doubling of the ALT value at reexposure as compared to the ALT value at baseline prior to reexposure. Second, reported methods to assess causality in the eight cases were evaluated, and then the liver specific Council for International Organizations of Medical Sciences (CIOMS) scale validated for hepatotoxicity cases was used for quantitative causality reevaluation. This scale consists of various specific elements with scores provided through the respective case data, and the sum of the scores yields a causality grading for each individual case of initially suspected hepatotoxicity.

RESULTS: Details of positive reexposure test conditions and their individual results were scattered in virtually all cases, since reexposures were unintentional and allowed only retrospective rather than prospective assessments. In 1/8 cases, criteria for a positive reexposure were fulfilled, whereas in the remaining cases the reexposure test was classified as negative (n = 1), or the data were considered as uninterpretable due to missing information to comply adequately with the criteria (n = 6). In virtually all assessed cases, liver unspecific causality assessment methods were applied rather than a liver specific method such as the CIOMS scale. Using this scale, causality gradings for Herbalife in these eight cases were probable (n = 1), unlikely (n = 4), and excluded (n = 3). Confounding variables included low data quality, alternative diagnoses, poor exclusion of important other causes, and comedication by drugs and herbs in 6/8 cases. More specifically, problems were evident in some cases regarding temporal association, daily doses, exact start and end dates of product use, actual data of laboratory parameters such as ALT, and exact dechallenge characteristics. Shortcomings included scattered exclusion of hepatitis A-C, cytomegalovirus and Epstein Barr virus infection with only globally presented or lacking parameters. Hepatitis E virus infection was considered in one single patient and found positive, infections by herpes simplex

virus and varicella zoster virus were excluded in none.

CONCLUSION: Only one case fulfilled positive reexposure test criteria in initially assumed Herbalife hepatotoxicity, with lower CIOMS based causality gradings for the other cases than hitherto proposed.

Key words: Herbalife hepatotoxicity; Herbalife induced liver injury; Herbal hepatotoxicity; Herb induced liver injury; Herbs

Core tip: Our analysis focuses on published cases of suspected Herbalife hepatotoxicity with positive reexposure tests and high causality gradings. Problems included poorly fulfilled test criteria, numerous confounding variables, and the use of liver unspecific, obsolete causality assessment methods. Submitting the case data to well established criteria for positive reexposure tests, the test was positive in 1/8 cases and negative or uninterpretable in the other cases. Using the liver specific Council for International Organizations of Medical Sciences scale, causality was probable in 1 case, unlikely and excluded in the other cases. Thus, causality levels were much lower than hitherto proposed.

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INTRODUCTION

Considerable interest focused on the question whether few Herbalife products are potentially hepatotoxic like some other herbal products and dietary supplements[1-10]. These reports created safety concerns and led to editorials[11-13], commentaries[14-16], and critical Letters to the Editor[17-27], all addressing relevant issues[11-27]. Speculations about bacterial contamination with *Bacillus subtilis* in Herbalife products emerged[8,12], and potentially hepatotoxic ingredients such as green tea extracts, *ephedra sinica*, aloe, or vitamin A overdose have been proposed as culprits[2-4,10]. In addition, overall case data quality was mixed due to confounding variables, missing firm exclusion of alternative explanations, and the use of problematic causality attribution methods[1-10]. For hepatotoxicity cases, even with stringent causality assessment the culprits remain undetected in up to 38% of severe liver disease[28], and alternative causes are frequently found[16,29,30], with up to 47% in initially assumed drug induced liver injury (DILI) cases[16,29] and with an average of 49% in initially suspected herb induced liver injury (HILI) cases[30].

When adjusted for case duplications, Herbalife hepatotoxicity was suspected in 53 cases[1-10]. Among these were eight cases with high causality gradings for Herbalife products because of positive unintentional reexposure tests, though criteria to evaluate reexposure tests were not presented[1-5]. A positive reexposure test is commonly considered as gold standard to establish causality for hepatotoxicity[1-5,31-35], provided specific and well established criteria are fulfilled[31-34]. A preliminary study revealed that in 17/30 cases of herbal hepatotoxicity with initially positive reexposure tests the presented data did not fulfil core criteria of a positive reexposure test or that the quality of case data was insufficient and led to uninterpretable results[16].

In this study, case data with assumed Herbalife hepatotoxicity and a positive unintentional reexposure test were reevaluated for fulfilment of specific and well established reexposure criteria and for liver specific causality assessments.

MATERIALS AND METHODS

Patients

We searched the Medline database for the terms "Herbalife hepatotoxicity" and "Herbalife induced liver injury" and retrieved ten publications; 53 cases were identified after adjustment for duplications[1-10]. Details were provided in case reports and case series of hepatotoxicity with assumed causal relationship to Herbalife products. In eight patients, a positive reexposure test with Herbalife was reported[1-5] with causality levels of highly probable[1], certain[2,3], likely and certain[4], and definite and probable[5]. These eight cases represented the study group.

Methods

All data sets of the eight patients with suspected Herbalife hepatotoxicity and positive reexposure tests were analyzed for specific criteria to establish a positive test result according to the conclusions of an international consensus meeting[31]. Some prerequisites are necessary to ensure transparency and reproducibility of this method. First, a baseline alanine aminotransferase (ALT) value < 5 upper limit of normal (N) is required after the first exposure and before the reexposure, with N as the upper limit of the normal range. Second, during reexposure the ALT value must be at least doubled as compared to the baseline ALT value before reexposure. Only when both criteria are met, a positive reexposure test can be assumed, otherwise the test is negative; the test is uninterpretable, if required information is not presented. Validated reexposure tests meeting the specific criteria are included in the Council for International Organizations of Medical Sciences (CIOMS) scale[32,34]. Time to onset of increased liver values after reexposure should be 1-15 d rather than ⩾ 16 d, thus providing additional strengths[31,32,34].

Causality assessment methods as reported in the eight Herbalife cases were evaluated in detail. Subsequently, causality was reevaluated using the quantitative, liver specific and structured CIOMS scale validated for hepatotoxicity[32] and its update as algorithm for hepatotoxicity causality assessment[34]. Causal relation to hepatotoxicity

requires ALT and/or alkaline phosphatase (ALP) values to be at least 2 N[32,34]; the type of injury was assessed as described, since a specific damage pattern is essential for further causality assessment[32]. To differentiate between the hepatocellular, cholestatic or mixed hepatocellular-cholestatic type of hepatotoxicity, serum ALT and ALP values are to be evaluated on the day the diagnosis of Herbalife hepatotoxicity was suspected. Each activity is expressed as a multiple of N, and the ratio (R) of ALT/ALP is calculated. Hepatocellular liver injury is assumed if ALT > 2 N with normal ALP, or R $\geqslant$ 5; cholestatic liver injury is assumed if there is an increase of ALP > 2 N with normal ALT or R $\leqslant$ 2; mixed cholestatic-hepatocellular type of liver injury is assumed in all other cases, *i.e.,* ALT > 2 N, ALP is increased with R > 2 and R < 5. Separate CIOMS scales are designed for either the hepatocellular type of liver injury or the cholestatic ($\pm$ hepatocellular) type[32,34].

RESULTS

Characteristics of the study group

The age of the eight patients ranged from 30 to 78 years (average 51 years) (Table 1). The female: male ratio was 7:1. Two patients originated from Switzerland (cases 1 and 5), three patients from Israel (cases 2-4), one patient from Iceland (case 6), and two patients from Spain (cases 7 and 8). Outcome was favourable in all patients. For each individual patient, all available details for the analysis of reexposure tests and causality assessments are listed (Table 1).

Most quality problems with missing data occurred in retrospective case series, and uncertainties to exclude or verify alternative causes remained from nonspecific parameters used. Available data was incomplete regarding case descriptions, daily doses, exact start and end dates of product use, actual values of laboratory parameters such as ALT, and exact dechallenge characteristics (Tables 1 and 2). In some cases, Herbalife consumption was described as "along the manufacturer's recommendations". In none of the cases was the daily dose of the Herbalife product quantified (Tables 1 and 2). Though exact start and end dates of Herbalife intake and onset of symptoms or increased liver values were missing in all cases, time on Herbalife and time to onset was available. Temporal association between Herbalife use and liver disease was present in all but one patient (case 5) (Table 2); in this patient, lack of temporal association results in lack of causal association (Table 1). In addition, actual data of laboratory parameters such as ALT with exact results and dates were rarely provided and raised questions about the dechallenge characteristics (Tables 1 and 2). Finally, comedication by drugs and/or herbs as confounding variable was reported in 6/8 cases (75%) (Table 2), but details about daily doses and duration of comedications were scattered and complicated clear causality attribution to comedication.

Core criteria to confirm or exclude alternative causes rely on abdominal and hepatobiliary tract imaging, but results were scattered and poorly provided in at best five of the eight patients (Tables 1 and 2). Abdominal ultrasound revealed cholecystolithiasis in one patient (case 1); however, imaging conditions were difficult, liver, gall bladder wall, extrahepatic bile ducts, and pancreas were not evaluated in this particular case (Table 1). Abdominal ultrasound was reported as normal and without evidence for non alcoholic fatty liver disease in three patients (cases 2-4), though details of gallbladder, bile ducts, and pancreas were missing (Table 1). In another patient (case 5) with chronic hepatitis E virus (HEV) infection, abdominal ultrasound was probably performed but data were not provided (Table 1). For all patients of this case series, exclusion of obstructive or tumorous liver disease by appropriate imaging techniques was described, usually by ultrasound imaging. In case 6, "tests did not indicate any other liver disease", but no technical details were specified, and extrahepatic causes were not excluded (Table 1). In two additional patients (cases 7 and 8), abdominal ultrasound was not reported (Table 1). Overall, abdominal ultrasound examinations were either poorly documented or lacking in these eight patients, making exclusion of alternative causes difficult.

In virtually none of the eight patients hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections were excluded by specific tests like anti-HAV-immunoglobulin M (IgM), hepatitis B surface antigen, anti-HBc IgM, HBV-DNA, anti-HBc-IgM, anti-HCV, and HCV-RNA (Table 1). However, vague descriptions were provided such as: "the hepatitis serology (HAV, HBV, HCV) gave no clue for an acute viral hepatitis" (case 1); "investigation for causes of liver damage included viral entities (hepatitis A, B, C viruses)" (cases 2-4); "exclusion of hepatitis A, B, C" (case 5); "tests did not indicate other liver diseases" (case 6); no statement regarding viral serology at all (case 7); and "negative viral serology" (case 8) (Table 1). Though confounding variables prevail and uncertainty exists, it was assumed in favour of the reports that hepatitis A, B, and C was excluded to a major extent in cases 1-5 but not in cases 6-8 (Table 2). Hepatitis E virus infection was considered and found in one patient (case 5) but not reported for the remaining seven patients (Tables 1 and 2). Exclusion of cytomegalovirus (CMV) and Epstein Barr virus (EBV) infection without specific parameters was reported in four patients (cases 1-4), and of herpes simplex virus (HSV) and varicella zoster virus (VZV) infection in none (Tables 1 and 2). Thus, these confounding variables are to be considered for causality assessment in assumed Herbalife hepatotoxicity.

Analysis of reexposure tests

Based on the specific criteria of reexposure tests for the hepatocellular type of liver injury (Table 3), the modalities of unintentional reexposure tests have been described and analyzed in detail for all eight cases (Table 4). Criteria for a positive reexposure test were fulfilled for only one patient (case 1), reexposure was negative

Table 1 Clinical data of all eight patients with liver disease and a reported positive reexposure test by Herbalife products

Patient	Identification	Specific information for each individual patient
1	Hoffmann *et al*[1], 63 yr female	Herbalife product of unknown daily dose for several weeks. BMI 30. Intended weight loss of 14 kg within the past 3 mo. Loss of appetite, nausea, vomiting, and abdominal crampy pains for 2 wk prior to first presentation with increasing jaundice, pale stool and dark urine, transient urticarial exanthema. Comedication: hydrochlorothiazide/amiloride for hypertension since 2 yr and celecoxib temporarily for relapsing vertebral pain syndrome. ALT 1897 U/L, AST 2098 U/L, ALP 248 U/L. Upon discontinuation of all drugs and Herbalife, ALT 35 U/L within 2 mo. Four weeks later, recurrent ALT increase with peak ALT 758 U/L under Herbalife reexposure, but duration of use not communicated and clear temporal association not evaluable. Exclusion of acute infection by HAV, HBV, HCV, CMV, and EBV reported, but details of parameters not communicated. HEV, HSV, and VZV not excluded. Pancreatitis not excluded. Slightly increased ANA and AMA. Difficult assessment conditions: abdominal ultrasound showed cholecystolithiasis, but number of stones and exclusion of cholecystitis and bile duct obstruction not reported, and magnetic resonance cholangiography not performed. Liver histology with acute cholestatic hepatitis, inflammatory biliary lesions, confluent necroses, and eosinophilic infiltration. For the first clinical episode, therefore, synthetic drugs, Herbalife, symptomatic cholecystolithiasis with crampy abdominal pains and possible transient choledocholithiasis, or an incipient overlap syndrome may have been responsible; for the second episode, Herbalife, the biliary disease, and an incipient overlap syndrome remain as culprits. For Herbalife, CIOMS 7 points Final diagnosis: Probable Herbalife hepatotoxicity, symptomatic biliary stone disease, or incipient overlap syndrome as less probable alternatives
2	Elinav *et al*[2], their case 1, 55 yr female	Herbalife products of unknown daily dose for 6 mo. BMI 33. Comedication: aspirin, metformin for non-insulin dependent diabetes mellitus, statins for hyperlipidemia. Lack of reported symptoms and actual data of ALT, AST, and ALP values initially and later on. Following first exposure, medications and Herbalife were stopped, resulting in complete recovery without any described details. One month after Herbalife reuse, a second flare of hepatitis was reported without any details, except that steroid treatment was initiated, which modulated the natural course. Together with Herbalife cessation, this resulted in complete recovery. Serology of HAV, HBV, HCV, CMV, and EBV was negative but not further specified and no reported serology for HEV, HSV, and VZV. Normal abdominal ultrasound. For Herbalife, CIOMS 2 points Final diagnosis: Unlikely Herbalife hepatotoxicity
3	Elinav *et al*[2], their case 2, 48 yr female	Herbalife products of unknown daily dose for 9 mo. BMI 32. Comedication: alpha adrenergic blocker for hypertension of unknown daily dose and treatment duration. Symptoms and actual values of ALT, AST, and ALP not reported. Resolving hepatitis following Herbalife cessation, but missing supportive data. A month after discharge reuse of Herbalife with a second episode, but liver values or further details not communicated. Serology of HAV, HBV, HCV, CMV, and EBV was negative but not further specified and no reported serology for HEV, HSV, and EBV. Normal abdominal ultrasound. Liver histology: hepatocellular hepatitis. For Herbalife CIOMS 1 point Final diagnosis: Unlikely Herbalife hepatotoxicity
4	Elinav *et al*[2], their case 12, 78 yr female	Herbalife products of unknown daily dose for 12 mo. BMI 27. Comedication: biphosphonates and aspirin of unknown daily dose and duration, background illness psoriasis and non insulin dependent diabetes mellitus. Lack of reported symptoms and of ALT, AST, and ALP initially and later on. Serology of HAV, HBV, HCV, CMV, and EBV was negative but not further specified and no reported serology for HEV, HSV, and VZV. Normal abdominal ultrasound. A second hepatitis flare developed after Herbalife reuse, but details not provided except that the hepatitis was unresolved at the time of manuscript submission. For Herbalife, CIOMS 2 points Final diagnosis: Unlikely Herbalife hepatotoxicity
5	Schoepfer *et al*[3], their case 1, 30 yr male	Herbalife products for 26 mo according to the manufacturer's recommended dose (exact daily dose not communicated). BMI 33. Painless jaundice as symptom. Reported initial liver enzymes as fold upper limit of normal: ALT 50, AST 19, and ALP 1.8, but lack of actual values in the subsequent course. Lack of any specific parameters and data on HAV, HBV, HCV, CMV, EBV, HSV, and VZV. Data for abdominal ultrasound not reported. Patient recovered from the first episode, but details of ALT values not provided and Herbalife cessation not communicated. At a second episode of jaundice, positive hepatitis E IgG antibodies. Liver histology showed acute hepatitis with dense neutrophilic and lymphocytic infiltration, multiple apoptotic bodies, and discrete endophlebitis of central veins. The pathologist considered these findings compatible with hepatitis E. Histology at a third episode showed also fibrosis and incomplete cirrhosis. Only after this third episode, the patient was advised to stop his intake of Herbalife products. Between the three episodes and around a fourth episode, normalization of ALT has never been documented, nor a real reexposition after a period of Herbalife cessation. Thus, chronic hepatitis E with incomplete cirrhosis and undulating liver values is the more likely diagnosis rather than Herbalife hepatotoxicity. For Herbalife, CIOMS -1 point Final diagnosis: Chronic hepatitis E, excluded Herbalife hepatotoxicity
6	Jóhannsson *et al*[4], their case 4, 44 yr female	Herbalife products of unknown daily dose for 5-6 mo. BMI unknown. Abdominal pain and jaundice as symptoms with a latency period of 4-5 mo. Comedication: bupropion of unknown daily dose for 20 d. ALT 2637 U/L, ALP 231 U/L. After stopping Herbalife and bupropion, normal liver values reported but details and time course not presented. Following Herbalife reuse, rise in liver values without any further details and normalization after 2 mo. Tests did not indicate any other liver disease, but no details described. Poorly documented case. For Herbalife, CIOMS -2 points Final diagnosis: Excluded Herbalife hepatotoxicity
7	Manso *et al*[5], their case 12, 39 yr female	Herbalife products of unknown daily dose for 60 d. Unknown BMI. No comedication. ALT 1200 U/L, AST 394 U/L, and ALP 454 U/L. Hepatitis improved after Herbalife cessation, but details of ALT values and time course not reported. Shortly after Herbalife rechallenge, recurrent increase of ALT with normalization after Herbalife withdrawal, but actual ALT values and time course not presented. No viral serology, no abdominal ultrasound. Insufficiently documented case. For Herbalife, CIOMS 1 point Final diagnosis: Unlikely Herbalife hepatotoxicity

8	Manso *et al*[5], their case 20, 49 yr female	Herbalife products of unknown daily dose for 2 yr. Unknown BMI. Comedication: Bach flowers. ALT 922 U/L, AST 702 U/L, ALP 201 U/L. Upon cessation of Herbalife and Bach flowers, ALT 793 U/L within 21 d. Eight days after Herbalife reintroduction, ALT 1500 U/L with lack of ALT normalization following Herbalife recessation. Negative viral serology reported, but no details presented. Abdominal ultrasound data not reported and obviously not done. Insufficiently documented case. For Herbalife, CIOMS 0 points Final diagnosis: Excluded Herbalife hepatotoxicity

Details are presented for eight patients with liver disease and a published positive reexposure test to Herbalife products. ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMA: Antimitochondrial antibodies; ANA: Antinuclear antibodies; AST: Aspartate aminotransferase; BMI: Body mass index in kg/m^2; CIOMS: Council for International Organizations of Medical Sciences; CMV: Cytomegalovirus; EBV: Epstein Barr virus; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; HSV: Herpes simplex virus; VZV: Varicella zoster virus.

Table 2 Overview of known information of eight cases with suspected Herbalife hepatotoxicity and positive reexposure tests

Presented information	Cases	Individual cases
Daily dose	0/8	-
Exact date of Herbalife start	0/8	-
Exact date of Herbalife end	0/8	-
Exact date of symptoms	0/8	-
Time on Herbalife	8/8	1, 2, 3, 4, 5, 6, 7, 8
Time to onset	8/8	1, 2, 3, 4, 5, 6, 7, 8
Temporal association	7/8	1, 2, 3, 4, 6, 7, 8
Specific symptoms	3/8	1, 5, 6
ALT value	5/8	1, 5, 6, 7, 8
AST value	4/8	1, 5, 7, 8
ALP value	5/8	1, 5, 6, 7, 8
ALT dechallenge	3/8	1, 7, 8
ALT normalization	1/8	1
Hepatobiliary tract imaging	5/8	1, 2, 3, 4, 5
HAV	5/8	1, 2, 3, 4, 5
HBV	5/8	1, 2, 3, 4, 5
HCV	5/8	1, 2, 3, 4, 5
HEV	1/8	5
CMV	4/8	1, 2, 3, 4
EBV	4/8	1, 2, 3, 4
HSV	0/8	-
VZV	0/8	-
Drug comedication	5/8	1, 2, 3, 4, 6
Herbal comedication	2/8	6, 8
Liver histology	3/8	1, 3, 5

Data are derived from the eight cases with details described in Table 1. Time to onset indicates time to symptoms, alternatively to abnormal liver tests. Alanine aminotransferase (ALT) dechallenge and ALT normalization refers only to cases with presented actual ALT values. ALP: Alkaline phosphatase; AMA: Antimitochondrial antibodies; ANA: Antinuclear antibodies; AST: Aspartate aminotransferase; BMI: Body mass index in kg/m^2; CIOMS: Council for International Organizations of Medical Sciences; CMV: Cytomegalovirus; EBV: Epstein Barr virus; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; HSV: Herpes simplex virus; VZV: Varicella zoster virus.

in another patient (case 8) (Table 4). In the remaining six patients (cases 2-7), exact ALT values before and at reexposure were only partially or not at all documented, leaving these cases uninterpretable. Two additional cases were presented with questionable positive reexposure test upon first look (Table 4); analysis showed lack of any evidence for a positive test.

Causality assessment

Liver unspecific causality assessment methods were applied in case 1 using the ad hoc approach and World Health Organization (WHO) global introspection method, in short WHO method, cases 2-5 (WHO method), case 6 (WHO method, combined with the liver specific CIOMS scale), and cases 7 and 8 (Karch and Lasagna method).

Table 3 Criteria of a positive reexposure test in herb induced liver injury cases

Test result	ALTb	ALTr
Positive	< 5 N	⩾ 2 ALTb
Negative	< 5 N	< 2 ALTb
Negative	⩾ 5 N	⩾ 2 ALTb
Negative	⩾ 5 N	< 2 ALTb
Negative	⩾ 5 N	N/A
Uninterpretable	< 5 N	N/A
Uninterpretable	N/A	N/A

Details and criteria for a positive reexposure test are based on the conclusions of International Consensus Meetings. Accordingly, required data are the alanine aminotransferase (ALT) levels just before reexposure, designated as baseline ALT or ALTb, and the ALT levels during reexposure, designated as ALTr. Response to reexposure is positive, if both criteria are met: first, ALTb is < 5 N with N as the upper limit of normal, and second ALTr ⩾ 2 ALTb. Other variations lead to negative or uninterpretable results. Criteria are based on ALT values and thereby applicable to the hepatocellular type of liver injury. N/A: Not available.

Causality for Herbalife was reevaluated using the updated CIOMS scale for the hepatocellular type of liver injury (Table 5), and identical results were obtained with the original CIOMS scale (data not shown). Considering previous information on assumed hepatotoxicity by Herbalife, all eight cases were credited uniformly with +1 point to simplify assessment. The overall scores ranged from +7 to -2 points, representing a broad spectrum of causality gradings. Causality levels for Herbalife were probable (case 1), unlikely (cases 2, 3, 4 and 7), and excluded (cases 5, 6 and 8).

For most cases, the scores were low (Table 5). In 7/8 cases, the latency period until symptoms or increased liver values appeared > 90 d, resulting in only +1 point rather the +2 points usually given in other HILI or DILI cases. ALT dechallenge often was poorly documented without actual values at day 8 and around day 30, resulting in 0 points. Comedication was reported in 6/8 cases, deducting 2 points in five cases. For exclusion of non-Herbalife causes, data quality was poor and resulted in +1 point in four cases and negative points in the remaining cases. Considering previous information on Herbalife hepatotoxicity, all eight cases were uniformly credited with +1 point, since no attempt was made in any of the

Table 4 Analysis of positive reexposure tests in cases with suspected Herbalife hepatotoxicity

Cases with initially suggested positive reexposure tests
Case 1
The 63-yr old woman used a Herbalife product and experienced a positive reexposure test that was fairly well documented, but duration of product reuse was insufficiently communicated[1]. Upon first challenge, ALT was 1897 U/L and declined to 35 U/L after product discontinuation. Rechallenge increased ALT 758 U/L. Since ALTb is < 5 N and ALTr ⩾ 2 ALTb, this ascertains the positive reexposure test
Case 2
The 55-yr old woman consumed Herbalife products. Liver disease by not further specified liver values as well as a positive reexposure test was described[2]. Individual ALT values were not presented, hence data required for criteria of ALTb < 5 N and ALTr ⩾ 2 ALTb are not available. The data are uninterpretable regarding the claimed positive reexposure test
Case 3
The 48-yr old woman was on Herbalife products, when hepatocellular hepatitis was diagnosed associated with a positive reexposure test[2]. Lack of any specific ALT values prevented establishing criteria of ALTb < 5 N and ALTr ⩾ 2 ALTb. The case is uninterpretable with respect to the reexposure test
Case 4
The 78-yr old woman used Herbalife products and was diagnosed with hepatocellular liver injury based on liver values[2]. A positive reexposure test was described, but details of the test and individual ALT values were not provided. Therefore, criteria of ALTb < 5 N and ALTr ⩾ 2 ALTb cannot be ascertained. The case is uninterpretable due to lacking test criteria.
Case 5
The 30-yr old man consumed Herbalife products and experienced a biopsy proven liver disease[3]. A positive reexposure test was described, but details were not provided. An initial ALT value was reported with lack of ALT data in the further course including the reexposure test, preventing the confirmation of the essential criteria ALTb < 5 N and ALTr ⩾ 2 ALTb. Lack of these criteria leads to uninterpretable data of the test
Case 6
The 44-yr old woman used Herbalife products, experienced jaundice with increased ALT 2637 U/L[4]. Following product cessation, normalization of liver values reported, but actual ALT values were not presented. After Herbalife reuse, rise of liver values was communicated, but no details of actual ALT values given. ALTb is probably < 5 N, but ALTr is unknown. Currently, this case is uninterpretable regarding the reexposure test
Case 7
The 39-yr old woman was on Herbalife products and experienced a hepatitis, which improved after product cessation, but actual ALT values before reexposure are not communicated[5]. Recurrent increase of ALT was reported, but actual values not presented. Since ALTb and ALTr are unknown, the reexposure test is uninterpretable
Case 8
The 49-yr old woman used Herbalife products and experienced an ALT of 922 U/L, which dropped after product cessation to 793 U/L and rose to 1500 U/L after reintroduction[5]. ALTb is ⩾ 5 N and ALTr < 2 ALTb, the test is negative
Cases with initially questionable positive reexposure tests
The 60-yr old man was reported with use of Herbalife products, a histology proven liver disease, and a questionable positive rechallenge[3]. When an increase of liver values was again observed, the patient denied Herbalife consumption. Thus, no evidence for a positive reexposure test exists
The 41-yr old woman was on a Herbalife product and suffered from fulminant hepatic failure requiring liver transplantation[3]. A questionable positive reexposure test with slightly elevated liver enzymes lacking actual ALT values was described for the transplanted liver one year after transplantation, when the patient was vague about Herbalife use. Therefore, clear evidence for a positive reexposure test is missing

The eight cases correspond to those presented in Table 1, and the data of the two cases with initially questionable positive reexposure tests are derived from the literature. Required data are alanine aminotransferase (ALT) levels at baseline before reexposure, designed ALTb, and ALT levels during reexposure, designed ALTr. Response to reexposure is positive, when ALTb < 5 N and ALTr ⩾ 2 ALTb. Criteria are applicable for the hepatocellular type if liver injury. N: Upper limit of normal.

individual published cases to differentiate whether one of the used Herbalife products had been considered as potentially hepatotoxic before. Unintentional Herbalife readministration with a positive and validated reexposure result provided +3 points in one patient and no point in the remaining seven patients due to a negative reexposure test result or uninterpretable data.

DISCUSSION

Reports of positive unintentional reexposure tests in eight cases of assumed hepatotoxicity by Herbalife products initially led to a high suspicion level of liver injury for these dietary supplements; however, specific criteria for the reexposure tests and liver specific causality assessment methods were not applied[1-5]. Using specific and established criteria for reexposure tests (Table 3)[16,31], reexposure results in the study group were positive in one patient, negative in another patient, and uninterpretable in six patients (Table 4). Subsequent liver specific causality assessments using the CIOMS scale showed much lower causality levels than published before; they now were probable (n = 1), unlikely (n = 4), or even excluded (n = 3) (Tables 1 and 5). For evaluating future cases with hepatotoxicity upon reexposure, the combined use of specific criteria for reexposure tests and liver specific causality assessment methods such as the CIOMS scale are the preferred tools to achieve valid results.

Generally accepted hepatotoxicity biomarkers for all cases are lacking; when available, a positive unintentional reexposure test is still considered as a gold standard to establish causality in DILI and HILI cases[16,32-35]. Retrospective assessment of unintentional reexposure tests is cumbersome, because clinical conditions are variable, as shown in the present report (Tables 1 and 4)[1-5] and in previous case analyses[14,36-51]. Specific criteria for reexposure tests are available since 1988 (Table 3)[31] and have been incorporated in the CIOMS scale (Table 4)[16,32,34] following successful use for validation purposes[33]. For the eight cases of assumed Herbalife associated hepato-

Table 5 Causality assessment of all eight patients with primarily suspected Herbalife hepatotoxicity and an initially assumed positive reexposure test

Items for hepatocellular type of injury	Score	1	2	3	4	5	6	7	8
1 Time to onset from the beginning of Herbalife									
5-90 d (rechallenge: 1-15 d)	+2							+2	
< 5 or > 90 d (rechallenge: > 15 d)	+1	+1	+1	+1	+1	+1	+1		+1
Alternative: Time to onset from cessation of Herbalife									
≤ 15 d (except for slowly metabolized chemicals: > 15 d)	+1								
2 Course of ALT after cessation of Herbalife									
Percentage difference between ALT peak and N									
Decrease ≥ 50% within 8 d	+3								
Decrease ≥ 50% within 30 d	+2	+2							
No information	0		0	0	0	0	0	0	0
Decrease ≥ 50% after the 30th d	0								
Decrease < 50% after the 30th d or recurrent increase	-2								
3 Risk factors									
Alcohol use (drinks/d: > 2 for woman, > 3 for men)	+1								
Alcohol use (drinks/d: ≤ 2 for woman, ≤ 3 for men)	0	0	0	0	0	0	0	0	0
Age ≥ 55 yr	+1	+1	+1		+1				
Age < 55 yr	0			0		0	0	0	0
4 Concomitant drug(s)									
None or no information	0					0		0	
Concomitant drug with incompatible time to onset	0								0
Concomitant drug with compatible or suggestive time to onset	-1								
Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset	-2	-2	-2	-2	-2		-2		
Concomitant drug with evidence for is role in this case (positive rechallenge or validated test)	-3								
5 Search for non Herbalife causes									
Group Ⅰ (6 causes)									
Anti-HAV-IgM		-	-	-	-	-			
Anti-HBc-IgM/HBV-DNA		-	-	-	-	-			
Anti-HCV/HCV-RNA		-	-	-	-	-			
Hepato-biliary sonography/colour Doppler sonography of liver vessels/endosonography/CT /MRC		+	-	-	-	-			
Alcoholism (AST/ALT ≥ 2)		-	-	-	-	-		-	-
Acute recent hypotension history (particularly if underlying heart disease)		-	-	-	-	-			-
Group Ⅱ (6 causes)									
Complications of underlying disease(s), such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis, genetic liver diseases		-	-	-	-				-
Infection suggested by PCR and titer change for									
CMV (Anti-CMV-IgM/IgG)		-	-	-	-				
EBV (Anti-EBV-IgM/IgG)		-	-	-	-				
HEV (Anti-HEV-IgM/IgG)						+			
HSV (Anti-HSV-IgM/IgG)									
VZV (Anti-VZV-IgM/IgG)									
Evaluation of group Ⅰ and Ⅱ									
All causes - group Ⅰ and Ⅱ - reasonably ruled out	+2								
The 6 causes of group Ⅰ ruled out	+1	+1	+1	+1	+1				
5 or 4 causes of group Ⅰ ruled out	0								
Less than 4 causes of group Ⅰ ruled out	-2						-2	-2	-2
Non Herbalife cause highly probable	-3					-3			
6 Previous information on hepatotoxicity of Herbalife									
Reaction labelled in the product characteristics	+2								
Reaction published but unlabelled	+1	+1	+1	+1	+1	+1	+1	+1	+1
Reaction unknown	0								
7 Response to readministration									
Doubling of ALT with Herbalife alone, provided ALT below 5 N before reexposure	+3	+3							
Doubling of ALT with Herbalife and herb(s) or drug(s) already given at the time of first reaction	+1								
Increase of ALT but less than N in the same conditions as for the first administration									
Other situations	0		0	0	0	0	0	0	0
Total points for patients		+07	+02	+01	+02	-01	-02	+01	0

In all eight patients with initially suspected Herbalife hepatotoxicity (Tables 1 and 4), causality assessment for Herbalife was performed with the updated CIOMS scale for the hepatocellular type of liver injury. The symbol "-" denotes that the obtained result was negative and that of "+" was positive, whereas lack of a symbol indicates missing data. Regarding risk factor of alcohol use, 1 drink commonly contains about 10 g ethanol. Total points provide causality levels: ≤ 0, excluded; 1-2, unlikely; 3-5, possible; 6-8, probable; ≥ 9, highly probable. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CIOMS: Council for International Organizations of Medical Sciences; CMV: Cytomegalovirus; CT: Computer tomography; EBV: Epstein Barr virus; HAV: Hepatitis A virus; HBc: Hepatitis B core; HBsAg: Hepatitis B antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; HILI: Herb induced liver injury; HSV: Herpes simplex virus; MRC: Magnetic resonance cholangiography; N: Upper limit of normal; VZV: Varicella zoster virus.

toxicity, no information was available whether specific criteria were used to assess the reexposure result as positive (Table 4)[1-5].

Notably, intentional reexposure tests are obsolete due to high risks to the health of the patients. In the past, this kind of approach provided validated test results, since appropriate test conditions could be established prospectively, facilitating data evaluation. For decades, however, only unintentional reexposure test results with scattered data are available as evidenced in the present Herbalife study[1-5], allowing retrospective rather than prospective evaluation (Table 4). These data gaps influence the CIOMS scoring, with only the one patient receiving +3 points indicating a positive result (case 1), whereas all other patients scored 0 points for the reexposure item (cases 2-8) (Table 5). This low score is even more remarkable since the CIOMS scale will award +2 points for an appropriate rechallenge time to onset of 1-15 d, and +1 point when the time to onset is > 15 d[32,34]. In future case reports of hepatotoxicity, therefore, special care should be provided to appropriate use of accepted criteria for reexposure tests.

Data problems of reexposure cases are not confined to Herbalife products (Table 4) but represent a general problem extending to liver injury by all herbal drugs, dietary supplements and herbal products[14,36-51]. Analysis of 30 cases within the last three decades claiming a positive reexposure test revealed that in many cases detailed descriptions of the reexposure test and actual ALT values were lacking. This was most evident in short case reports, often presented as a letter to the editor, and in case series. In retrospect, a positive reexposure test has been confirmed in only 13/30 cases (43%)[16], as ascertained by established criteria published previously[31]. Of note, none of these reports communicated criteria for the evaluation of the observed reexposure test[14,16,36-51].

The use of inappropriate causality assessment methods in the analyzed case reports is difficult to reconcile[1-5]. An ad hoc approach was applied in one patient (case 1)[1], with reassessment[3] by the WHO method[52]. This method was also used in four other patients (cases 2-5) alone[2,3] or in one patient (case 6) combined with the CIOMS scale[4]. In the remaining patients (cases 7 and 8)[5], assessment was achieved with the Karch and Lasagna method[53]. None of these approaches except the CIOMS scale is liver specific; the methods are not validated for hepatotoxicity and obsolete under these conditions. Clear preference should have been given to the CIOMS scale, with all its strengths and weaknesses[16,31-35,54]. The CIOMS scale considers all core elements of hepatotoxicity (Table 5)[34]; it was developed by an international expert panel and validated by cases with positive reexposure tests as gold standard[32,33]. CIOMS based assessment has shown good sensitivity (86%), specificity (89%), and positive predictive value (93%) and negative predictive value (78%)[33].

Surprisingly, the WHO method[52] used in most of the analyzed studies[1-5] has not been validated for any adverse drug reaction[55,56], its global introspection by experts has been shown to be neither reproducible nor valid[57]; it is not reference validated or quantitative[52,54-61], and reliability, sensitivity, specificity, positive and negative predictive values are unknown[52,54-56,61]. Both the questions and the possible answers posed to the assessor are ambiguous[54,56]. Specifically, the assessor considers factors that might causally link one or more drugs to an observed adverse drug reaction (ADR), lists all factors, weighs their importance, and decides the probability of drug causation[57]; but no checklist is given or level of strength required. Its scope is also limited since it cannot discriminate between a positive and a negative correlation, thereby stimulating overdiagnosing and overreporting[52]. The WHO method ignores data uncertainties, *e.g.*, in daily dose, temporal association, start, duration, and end of herbal use, time to onset of the ADR, and course of liver values after herb discontinuation. Insufficiently considered or ignored are comedications, preexisting liver diseases, numerous alternative explanations, and exclusion of virus infections by hepatitis A-C, CMV, EBV, HSV, and VZV[56,59,60].

Also for case evaluation[5] by the old Karch and Lasagna method[53], subjective judgement is needed for many steps, making the method more prone to bias[35]. Though commonly applied by the Spanish Pharmacovigilance Centres[5], this method is not used by the Spanish Group for the Study of Drug-induced Liver Disease[14,35,62,63]. For unknown reasons, this group did not tabulate any of the suspected Spanish Herbalife cases together with HILI cases that had been assessed by the CIOMS scale[14].

Assessment of the suspected Herbalife cases revealed various shortcomings and possible confounders creating concern in the present study (Tables 1, 2, 4 and 5). This is a general problem in retrospective analyses[1-5], case collection from nationwide hospitals[2,3], and spontaneous reports derived from regulatory agencies[5], as are challenges of causality assessments in HILI cases[16,30,55,56,58-61,64-68]. In a recent comprehensive review article of herbal and dietary supplement hepatotoxicity, careful analysis included the use of the CIOMS scale, being the diagnostic tool of choice in the literature pertaining to herbal hepatotoxicity[68]. This is supported by an actual evaluation of 573 HILI cases, which showed that the CIOMS scale was applied in 275/573 cases (48%)[30]. Possible or likely alternative diagnoses were evident in 278/573 cases (48.5%) of suspected HILI cases; causality assessment was impeded in 165/573 patients (29.0%), resulting in diagnostic problems in 77.5% of all cases[30]. Given these limitations, actual discussions of suspected Herbalife hepatotoxicity are understandable regarding case data quality and the preferred tool to assess causality[69,70], issues also recognized before[16,30,34] and in the present study (Tables 1, 2, 4 and 5). In reference to three case series of suspected Herbalife hepatotoxicity from Israel[2], Switzerland[3], and Spain[5], the opinion has been expressed that these series have utilized generally accepted causality assessment for herbal hepatotoxicity[70]. In these three case series, causality assessment methods were the WHO method[52] in two series[2,3] and

the Karch and Lasagna method[53] in one series[5]. All these approaches are liver unspecific, not validated for hepatotoxicity cases, and therefore inappropriate tools assessing causality in HILI cases[16,30,56,59-61]. The National Institutes of Health LiverTox specifically addressed the item of causality in hepatotoxicity cases and focused primarily on using the CIOMS scale, whereas the WHO method and the Karch and Lasagna method were not discussed and not even mentioned, thereby simply ignored[65,66], as in a careful review article published recently[68].

Incomplete data of viral serology in the present study (Tables 1, 2, and 5) is an issue also for DILI cases[71]. It may be of relevance for HEV infection, which is poorly tested but confirmed in one patient (Table 2) and easily overseen, as demonstrated in recent reports[72,73]. Carefully conducted studies have shown that 21% of patients with criterion-referenced DILI did not have DILI at all, but had HEV infection[72]. Similarly, among 318 patients with suspected DILI, 50 (16%) were tested positive for anti HEV IgG and nine (3%) for anti HEV IgM[73]. Moreover, 22% of patients with autochthonous hepatitis E were erroneously thought to have criterion-referenced DILI[72]. The authors comment and believe that these findings are likely to be applicable to other studies in the developed world and emphasize that DILI cannot securely be diagnosed without HEV testing and exclusion. This certainly also applies to suspected HILI cases.

In conclusion, the analysis of cases of initially assumed Herbalife hepatotoxicity with positive reexposure tests and high causality levels revealed both lacking criteria for the tests and missing use of a liver specific causality assessment method. Based on these shortcomings, causality levels for Herbalife had to be downgraded. Future assessment of liver injury by dietary supplements will require thorough evaluation of both unintentional reexposure tests by specific and established criteria and causality by liver specific methods.

COMMENTS

Background

Considerable interest focused on the question whether few Herbalife products are potentially hepatotoxic, but overall data quality of reported cases was mixed due to confounding variables and missing criteria for the firm exclusion of alternative explanation and/or a well-based causality attribution. For hepatotoxicity cases, stringent causality assessment is mandatory, since the culprit remains undetected in up to 38% of severe liver disease. Alternative causes are frequently found, with up to 47% in initially assumed drug induced liver disease, and with an average of 49% in initially suspected herb induced liver injury.

Research frontiers

A positive reexposure test is commonly considered as gold standard to establish causality for hepatotoxicity by drugs and herbs, but in published reports, test conditions and results rarely are presented with specific details. Therefore, in cases with assumed hepatotoxicity and a positive unintentional reexposure test, the question should be answered whether specific and well established reexposure criteria were fulfilled.

Innovations and breakthroughs

This is the first study that critically analyzes reported positive unintentional reexposure tests in initially suspected liver injury by herbal dietary supplements, using published criteria of the test.

Applications

The data can contribute to a more sophisticated and critical approach assessing results of an unintentional reexposure retrospectively, taking into account established test criteria.

Terminology

Positive reexposure test: Though commonly claimed as a gold standard to establish the diagnosis of liver injury by drugs and herbs, published reports usually lack any definition. For a positive reexposure test, a baseline value alanine aminotransferase (ALT) below 5 upper limit of normal (N) before reexposure is required, with N as the upper limit of the normal value, and a doubling of the ALT value at reexposure as compared to the ALT value at baseline. Reexposure tests are unintentional and require retrospective analysis of mostly scattered data. Though previously providing good results due to prospective assessment, intentional reexposure tests are obsolete to due high risks.

Peer review

The authors analyze the reported eight cases of assumed Herbalife hepatotoxicity with a positive unintentional reexposure test in this well conducted study. Various dietary supplements may cause liver injury. Therefore, it is interesting for determining whether there is a clear causality between some Herbalife products and hepatotoxicity. The analytical approaches are described in detail, the results are impressive.

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