Liver, Pancreas and Biliary Tract

Kava hepatotoxicity: Regulatory data selection and causality assessment

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ARTICLE INFO

ABSTRACT

Background: Kava hepatotoxicity in 20 patients from Germany has been debated worldwide following a regulatory ad hoc causality assessment and ban of kava, an anxiolytic herbal remedy obtained from the rhizome of *Piper methysticum* Forster.
Aims: We assessed causality with a quantitative structured causality analysis in all 20 cases of patients with liver disease, presented by the German regulatory agency that assumed a causal relationship with the use of kava extracts.
Methods: The quantitative scale of CIOMS (Council for International Organizations of Medical Sciences) in its updated form was employed for causality assessment and quality evaluation of the regulatory data presentation.
Results: The regulatory information is scattered and selective, and items essential for causality assessment, such as exclusion of kava independent causes, were not, or only marginally, considered by the regulator. Quantitative causality assessment for kava was possible ($n = 2$), unlikely ($n = 12$), or excluded ($n = 6$), showing no concordance with the regulatory ad hoc causality evaluation.
Conclusion: The regulatory data regarding kava hepatotoxicity is selective and of low quality, not supportive of the regulatory proposed causality; but instead, is an explanation of the overall causality discussions of kava hepatotoxicity. We are proposing that the regulatory agency reports data in full length and reevaluates causality.

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1. Introduction

Causality assessment of toxic liver disease by chemical drugs, herbal remedies and dietary supplements is a major challenge for health organisations and regulatory agencies [1–5]. Their databases commonly contain a substantial body of spontaneous reports which may be used for regulatory measures, even though different levels of causality are evident and data varies from one study to the other. For instance, causality could not be established in cases of drug-induced liver disease reported to the database of the WHO (World Health Organization) [1], was suggested by EMEA (European Medicine Agency) in only 4 out of 40 cases with liver disease in an assumed relationship with the treatment by black cohosh [2] but subsequently discussed [3], and was proposed by the German regulatory agency in 20 out of 38 patients with assumed hepatotoxicity by kava [4] but immediately debated as being flawed [5].

Kava hepatotoxicity has attracted great interest worldwide [5–24], since the use of kava was considered previously as safe and devoid of major side effects [5–9]. Kava (*Piper methysticum* G. Forster) is a perennial shrub native to islands of the South Pacific [6]. Its rhizome contains various psychoactive kavapyrones [5,14] and is used for preparation of aqueous, ethanolic and acetonic extracts [9]. Whereas aqueous kava extracts serve as beverages for informal social occasions and traditional ceremonials in most South Pacific islands [5,9], ethanolic and acetonic kava extracts are considered as herbal anxiolytic remedies [6] with proven efficacy according to a systematic Cochrane review [19].

Based on ad hoc causality assessments kava was declared by the German regulatory agency as being hepatotoxic in 20 patients from Germany, and a regulatory ban of kava extracts followed [4]. In face of the ongoing discussions regarding the quality of both the regulatory data presentation and the subsequent causality assessment [5–24], we have analysed the available published regulatory data and submitted these to a structured quantitative causality evaluation. We found that the regulatory data as published was selective and of low quality, and did not substantiate the regulatory causality assessment, but instead explained the overall discussions.

2. Patients and methods

The study consisted of 20 patients from Germany with liver disease declared by the German regulatory agency (BfArM, Bun-

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desinstitut für Arzneimittel und Medizinprodukte, Bonn) on an ad hoc basis, to be all causally related to the treatment by ethanolic and acetonic kava extracts [4]. Regulatory evaluation ranged from certain and probable, to possible causality. The individual data of each patient was presented online by the regulatory agency, and were now analysed regarding quality required for a sound causality assessment. Basically, the original regulatory data of patients with assumed kava hepatotoxicity were subjected to both a thorough ad hoc evaluation and a structured quantitative causality assessment.

In the initial stage, the ad hoc causality evaluation was cumbersome due to regulatory data shortage and incomplete signals provided by spontaneous reports [18]. Since the regulatory data appeared scattered and selective [4], additional details were asked for as outlined before [18]. When appropriate, the authors of published case reports [20–23], the involved pharmaceutical companies [18], and others [16,24] were kindly requested to supplement the regulatory presented data and to assure completeness as far as possible [18]. Most of the additional data including medical reports were provided to us by the reporting hospital physicians and the primary care physicians through the involved manufacturers. Thereby, a comparison of the ad hoc causality evaluation was attempted regarding the original regulatory data alone with those supplemented by additional features.

For the second evaluation step, the original regulatory data of each patient [4] was submitted item by item to a thorough assessment of the temporal as well as the causal association. The structured quantitative criteria of CIOMS published by Danan and Bénichou [25] were used in its updated form [26]. The CIOMS system was derived from an international concensus meeting of experts who defined various parameters such as time to onset, course of improvement of laboratory data, risk factors, concomitant drugs, searches for nondrug causes, previous information on hepatotoxicity of the drug, and response to re-administration [25]. It provides with each of these parameters a range of scores, and the total score is computed and may be divided into ranges that represent a causality being highly probable, probable, possible, unlikely or excluded. The CIOMS scale has been well validated (sensitivity 86%, specificity 89%, positive predictive value 93%, and negative predictive value 78%) [27] and is universally accepted [28–32]. It has been established by experts originating from France, Denmark, Germany, Italy, UK and USA [25] and was based on the results of rechallenge tests [27] considered as gold standard for the diagnosis of hepatotoxicity by drugs and dietary supplements [25,27]. The scale consists of two parts, one is available for the hepatocellular and the other one for the cholestatic ($\pm$ hepatocellular) type of acute toxic liver disease. Differentiation by laboratory tests is therefore a requisite for an evaluation [25]. Serum activities of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are measured on the day drug-induced hepatotoxicity is suspected. Each activity is expressed as multiple of the upper limit of the normal range (N), and the ratio (R) of ALT:ALP is calculated. Liver injury is (1) hepatocellular, when ALT > $2N$ alone or $R \geq 5$ (2), cholestatic, when there is an increase of ALP > $2N$ alone or when $R \leq 2$, and (3) of the mixed type, when ALT > 2, ALP is increased and $2 < R < 5$. When the available laboratory data of the 20 patients were assessed [18], a hepatocellular type of liver disease emerged rather than a cholestatic ($\pm$ hepatocellular) one.

Finally, with the third step of this study regarding the observed liver disease in assumed causal relationship for kava, various types of evaluation are principally evident: (1) present ad hoc causality assessment for kava, based merely on the original regulatory data; (2) present ad hoc causality evaluation for kava, based on the supplemented original regulatory data; (3) structured causality assessment for kava, based merely on the original regulatory data; and (4) comparison of the present study, using the ad hoc

and the updated CIOMS causality assessment, with the data of these 20 patients evaluated by other studies [4,7,16,18,24,33,34]. These comprise the ad hoc assessments for kava by BfArM [4], MCA (Medicine Control Agency) [7,16,24,33], EMEA [16,24,34], and Schmidt et al. [16,24] as well as the structured causality assessment for kava as completed study, using a bundle of information from various sources apart from the regulatory data [18].

Liver histology was available in 14 of 20 cases with a wide range of changes [18]. These include liver cell necrosis alone (cases 5, 7 and 11) and combined with hepatitis (cases 17 and 19), with hepatitis and intrahepatic cholestasis (case 20), with hepatitis and bile duct proliferation (case 1), with hepatitis, intrahepatic cholestastis and bile duct proliferation (case 3), with intrahepatic cholestasis (case 8), or with hepatitis, intrahepatic cholestasis and cholangitis (case 12). Other changes were described such as toxic hepatopathy with hepatic atrophy (case 4), lobular hepatitis (case 10), intrahepatic cholestasis and fibrosis (case 18), and intrahepatic cholestasis with signs of hypersensitivity (case 2).

3. Results

3.1. General characteristics of the study group

The information on all 20 patients is presented and includes age, gender, details of the treatment by kava extracts, co-medication and outcomes (Table 1). The patients were in the age of 23–81 years and mostly females. They had predominantly used ethanolic rather than acetonic kava extracts with often increased daily use of kavapyrones and/or prolonged duration of treatment outside the regulatory recommendations (60–120 mg kavapyrones daily for not longer than 3 months). Outcome was favourable in 13 patients, and in 4 others after LTX, but lethal in 3 patients including 2 subsequently due to LTX.

3.2. Regulatory data presentation and ad hoc causality assessment

In general, the original regulatory information of the 20 patients was selective and thereby inadequate (Table 1). No major regulatory attempt has been made to present, for instance, results concerning exclusion of non-kava and nondrug causes, and the ad hoc causality in most of the cases had to be considered primarily as unassessable for kava (individual data not shown). Although not presented by the regulator, important data substantiating causes independent from kava have been available and are now used together with the regulatory data, for ad hoc causality assessment (Table 1). The ad hoc causality for kava was not assessable in 8 and excluded in 10 patients, possible in one other and highly probable in another one (Table 1). Despite the shortcomings regarding regulatory data presentation, selection and major deletions, the regulatory ad hoc assessment for kava in patients with liver disease described a possible, probable or certain causality in all 20 patients. It therefore appears that the results of ad hoc causality assessments vary substantially, depending on quality of presented information, extent of the data selection and deletion of information essential for a sound evaluation.

3.3. Structured causality assessment

The regulatory data presented for each of the 20 patients were then subjected to a causality assessment for kava using the updated quantitative scores of CIOMS (Table 2). In 18 out of 20 patients the total points ranged from -1 to 2, rendering an excluded or unlikely causality for kava. The remaining 2 patients achieved a total of 3 points each, representing a low level of a possible causality (3–5

Table 1
Clinical data of all patients (*n* = 20) with regulatory suspected liver disease in assumed association with the treatment by kava extracts.

Patient	Identification	Age (years)	Sex	Kava extract	Duration of kava therapy (months)	Kavapyrones (mg/day)	Co-medication	Outcome (f = favourable, d = died)	Regulatory information/deletion	Present ad hoc causality assessment for kava	Regulatory ad hoc causality assessment for kava	Additional references
01	BfArM 93015209	38	f	Acetonic	3.5	210	Oral contraceptive, diazepam, L-thyroxine	f	Exclusion of non-kava causes not reported.	Unassessable	Probable	[7,16,24]
02	BfArM 94006568	68	f	Acetonic	24	210	St. John's wort, aluminium hydroxide	f	Exclusion of non-kava causes not communicated. Observed recurrent increase of ALT during kava discontinuation not mentioned and its relevance for kava unrelated causality (qualitative CIOMS assessment) not discussed. Existing increased ANA and AMA titres not mentioned. Alternative diagnosis of AIH and PBC or overlap syndrome not discussed.	Excluded	Possible	[7,16,18]
03	BfArM 94901308	50	f	Acetonic	1.5	210	Furosemide, atenolol, terfenadine	f	Exclusion of non-kava causes not documented. Existing recurrent increase of ALT during kava discontinuation not mentioned and its relevance for a kava unrelated causality (qualitative CIOMS assessment) not discussed. Existing increased HSV-IgM titre not reported and alternative diagnosis of herpetic hepatitis not evaluated.	Excluded	Probable	[7,16,18,24]
04	BfArM 98004297	81	f	Ethanolic	10	120	Hydrochlorothiazide, crataegus extract	d	Exclusion of non-kava causes not reported. Observed recurrent increase of ALT during kava discontinuation not mentioned and its relevance for kava unrelated causality (qualitative CIOMS assessment) not discussed. Existing increased titres of LKM antibodies not recorded and alternative diagnosis of LKM-AIH not evaluated.	Excluded	Probable	[16,18,24]

Table 1 (*Continued*)

Patient	Identification	Age (years)	Sex	Kava extract	Duration of kava therapy (months)	Kavapyrones (mg/day)	Co-medication	Outcome (f = favourable, d = died)	Regulatory information/deletion	Present ad hoc causality assessment for kava	Regulatory ad hoc causality assessment for kava	Additional references
05	BfArM 99006005	33	f	Ethanolic	4	180	Cisapride	f	Exclusion of non-kava causes not documented. Not further specified antibodies described and attributed to a kava induced AIH but not discussed regarding a genuine AIH.	Excluded	Probable	[7,16,18,24]
06	BfArM 99006200	35	f	Ethanolic	3	120	St. John's wort	f	Exclusion of non-kava causes not communicated and also not available. Nevertheless, the regulator states that non-kava causes are not evident.	Unassessable	Probable	[7,16]
07	BfArM 00005994 Saß et al. [20]	50	f	Ethanolic	7	60	Estrogens, gestagens, metformin, glimepiride, St. John's wort	LTX	Exclusion of non-kava causes not reported. Existing increased titres of EBV-IgM antibodies, ANA and SMA not mentioned and alternative diagnosis of EBV hepatitis, EBV-AIH or genuine AIH not discussed.	Excluded	Probable	[7,16,18,24]
08	BfArM 00008627 Brauer et al. [21]	23	f	Ethanolic	4	240	Rizatriptan, oral contraceptive	LTX, d	Exclusion of non-kava causes not documented. Observed recurrent increase of ALT during kava discontinuation not mentioned and its relevance for a kava unrelated causality (qualitative CIOMS assessment) not discussed. Existing increased titres of CMV-IgM antibodies not recorded and alternative diagnosis of CMV hepatitis not discussed.	Excluded	Probable	[7,16,18,24]
09	BfArM 01003950	48	f	?	?	?	?	f	Virtually no data reported. Brand name of the kava extract unknown. No information of time to onset from the beginning of kava and from cessation of kava presented. Course with actual ALT values not mentioned. Exclusion of non-kava causes not reported. Unclear case, not suitable as index case for a possible subsequent re-administration (see case 10, identical patient).	Unassessable	Certain	[7,16,24]

10	BfArM 01003951	56	f	Ethanolic ?	?	ʟ-Thyroxine, estradiol, omeprazole, losartan	f	Exclusion of non-kava causes only for HCV, CMV and EBV reported. No information of time to onset from the beginning of kava and from cessation of kava presented. Course with actual ALT values not given. ALT values just before questionable kava re-administration not presented. This case and the former one (identical patient) are unsuitable for assessment as a positive rechallenge test.	Unassessable	Certain	[7,16,24]
11	BfArM 01006229	32	m	Ethanolic 3	240	Valerian extract	LTX (2×)	Exclusion of non-kava causes incomplete, details also regarding hepatitis and AIH not presented. Recurrent increase of ALT during kava cessation not mentioned and its relevance for a kava unrelated causality (quantitative CIOMS assessment) not discussed. Existing increased AMA titres not reported and alternative diagnosis of PBC not discussed.	Excluded	Probable	[7,16,18]
12	BfArM 01006939	36	m	Acetonic 1.5	70	–	f	Exclusion of non-kava causes incompletely communicated, details also regarding virus and autoimmune genesis not reported. Existing hepato-splenomegaly, increased MCV and pancytopenia (anemia, leucopenia, thrombocytopenia) not mentioned and not evaluated regarding another underlying disease.	Excluded	Probable	[16]
13	BfArM 01010536	45	f	Ethanolic 4	45	Cynara scolymus extract	f	Exclusion of non-kava causes incompletely documented. The information that serological results were negative is not precise enough.	Unassessable	Probable	[16]

Table 1 (*Continued*)

Patient	Identification	Age (years)	Sex	Kava extract	Duration of kava therapy (months)	Kavapyrones (mg/day)	Co-medication	Outcome (f = favourable, d = died)	Regulatory information/deletion	Present ad hoc causality assessment for kava	Regulatory ad hoc causality assessment for kava	Additional references
14	BfArM 02000370	50	f	Ethanolic	3.5	240	Oral contraceptive, cyclandelat	f	Exclusion of non-kava causes incompletely documented. An infection and an autoimmune disease excluded without further details. Report came from pharmacist, not from treating physician who denied a possible causality for kava. Cryptogenic liver cirrhosis diagnosed in spring 1998, start with kava treatment 20.2.1998.	Unassessable	Possible	[16]
15	BfArM 02001414	46	f	Ethanolic	1	360	–	f	Exclusion of non-kava causes incompletely presented regarding specific parameters for hepatitis A–C and lack of HSV as well as ultrasonography results. Existing chronic epigastric pain, increased lipase and decreasing under i.v. infusion therapy, increased y-GT and ALP not mentioned, alternative diagnosis of pancreatitis not discussed.	Excluded	Probable	[16,18]
16	BfArM 02002090	26	f	Ethanolic	0.25	50	Sulfasalazine, diclofenac, progesterone, omeprazole, butylscopolaminium-bromide	f	Age not assessed by regulator but generally known. Exclusion of non-kava causes not documented.	Unassessable	Probable	[16,24]
17	BfArM 02002378	61	f	Ethanolic	3	120	Omeprazole, hymecromon, ginkgo biloba extract	LTX, d	Time to onset from cessation of kava not documented. Exclusion of non-kava causes not presented.	Unassessable	Probable	[7,16]

18	BfArM 02003010	48	f	Ethanolic 6	850	Silymarin, rheumeda (homeopathic preparation), gelum (mineral supplement), polilevo (amino acid complex)	LTX	Partial exclusion of non-kava causes with not clearly documented antibodies (HAV, HBV, HCV, CMV) and lack of ultrasonography results. Recurrent increase of ALT during kava discontinuation not mentioned and its relevance for a kava unrelated causality (qualitative CIOMS assessment) not discussed. Known regular alcohol consumption not documented and not discussed. Existing data of cirrhosis and fatty liver not mentioned and not discussed. Existing increased lipase and oedematous pancreatitis shown by ultrasound examination not reported and not discussed. Existing increased y-globulins and enhanced AMA titres not documented and not discussed regarding PBC as an alternative diagnosis.	Excluded	Possible	[16,18,24]
19	Strahl et al. [22]	39	f	Ethanolic 6	60	Oral contraceptive, paroxetine, St. John's wort	f	Exclusion of non-kava causes not presented. Existing positive rechallenge test reported.	Highly probable	Certain	[7,16,18,24]
20	Kraft et al. [23]	60	f	Ethanolic 12	1200	Etilefrine, piretanide	LTX	Exclusion of non-kava causes fairly well reported, except results of ultrasound examination, ANA and urinary copper excretion/24 h. BMI 31.8 kg/m^2 not mentioned.	Possible	Probable	[7,16]

The present ad hoc causality assessment for kava is based on all data provided by the regulator [4], now being supplemented by other existing information primarily deleted by the regulator but presented by additional references as outlined under regulatory information/deletion. A recurrent increase of ALT during kava cessation refers to a kava unrelated causality according to the qualitative CIOMS assessment [25]. The results of the regulatory ad hoc causality assessment for kava were published earlier [4]. For details see Section 2.

AIH denotes autoimmune hepatitis; AMA, antimitochondrial antibodies; ALT, alanine aminotransferase; ANA, antinuclear antibodies; BMI, body mass index; CIOMS, Council for International Organization of Medical Sciences; CMV, cytomegalovirus; EBV, Epstein Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; LKM, liver kidney microsomal antibodies; LTX, liver transplantation; MCV, median cell volume; PBC, primary biliary cirrhosis; SMA, smooth muscle antibodies.

Table 2

Causality assessment for kava in patients with liver disease ($n = 20$), using the updated quantitative score of CIOMS and all regulatory provided data of each patient. In section 7 (search for nondrug causes) the symbol of − denotes that the obtained result was negative and that of + was positive. Total points: ≤ 0 = causality excluded; 1–2 = causality unlikely; 3–5 = causality possible; 6–8 = causality probable; >8 = causality highly probable.

Causality item	Possible score	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. Time to onset from the beginning of the drug																					
5–90 days	+2	2		2	2		2					2	2			2	2	2			
<5 or >90 days	+1		1			1		1	1					1	1				1		1
2. Time to onset from cessation of the drug																					
≤15 days	+1	1	1	1	1	1	1	1	1			1	1	1	1	1	1	1	1	1	1
3. Course of ALT after cessation of the drug																					
Decrease ≥50% within 8 days	+3																				
Decrease ≥50% within 30 days	+2																				
No information	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Decrease ≥50% after the 30th day	0																				
Decrease <50% after the 30th day or recurrent increase	−2																				
4. Risk factor ethanol																					
Yes	+1																				
No	0	0		0	0								0								
5. Risk factor age																					
≥55 years	+1		1		1						1								1		1
<55 years	0	0		0			0	0	0	0		0	0	0	0	0				0	
6. Concomitant drug(s)																					
None or no information	0									0			0			0			0		
Concomitant drug with incompatible time to onset	0													0							
Concomitant drug with compatible or suggestive time to onset	−1		−1				−1					−1									
Concomitant drug known as hepatotoxin and with compatible or suggestive time to onset	−2	−2		−2	−2	−2		−2	−2		−2				−2		−2	−2		−2	−2
Concomitant drug with evidence for its role in this case (positive rechallenge or validated test)	−3																				
7. Search for nondrug causes																					
Group I (six causes)																					
Anti-HAV-IgM																					
Anti-HBc-IgM/HBV-DNA																−		−			−
Anti-HCV-IgM/HCV-RNA																−		−			−
Biliary obstruction (ultrasonography)													−			−		−			−
Alcoholism (AST/ALT ≥2)																					
Acute recent hypotension history (particularly if underlying heart disease)																					
Group II																					
Complications of underlying disease(s)																					
Clinical and/or biological context suggesting infection by																					
CMV (anti-CMV-IgM/PCR)																−					−
EBV (anti-EBV-IgM/PCR)																−		−		−	−
HSV (anti-HSV-IgM/PCR)																−		−			−

Left table (rotated; shown in original orientation):

	Score																				
		–2	2	2	–2	–2	–2	–2	–2	–2	–2	–2	–2	–2	–2	–2	–2	–2	–2	–2	2
																					3
																				0	
Evaluation of Groups I and II																					
All causes – groups I and II – reasonable ruled out	+2																				
The six causes of group I ruled out	+1																				
Five or four causes of group I ruled out	–0																				
Less than four causes of group I ruled out	–2																				
No drug cause highly probable	–3																				
8. Previous information on hepatotoxicity of the drug																					
Reaction labelled in the product characteristics	+2																				
Reaction published but unlabelled	+1																				
Reaction unknown	0																				
9. Response to re-administration																					
Doubling of ALT with the drug alone	+3																				
Doubling of ALT with the 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	–2																				
Other situations	0																				
Total points		1	2	1	2	2	2	2	2	0	2	0	0	0	–1	0	0	2	1	3	1

Details of the patients are given in Table 1.
ALT denotes alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; N, normal range (upper limit); PCR, polymerase chain reaction.

Table 3

Regulatory information about various items required for causality assessment in patients ($n = 20$) with liver disease in regulatory assumed causal relationship to kava treatment.

Causality item	Frequency of regulatory information
1. Time to onset from the beginning of the drug	17/20
2. Time to onset from cessation of the drug	18/20
3. Exact course of ALT after cessation of the drug	0/20
4. Risk factor ethanol evaluated	4/20
5. Risk factor age evaluated	19/20
6. Concomitant drug(s)	20/20
7. Search for nondrug causes	
Group I (six causes)	
More than three causes of group I ruled out	0/20
Anti-HAV-IgM	3/20
Anti-HBc-IgM HBV-DNA	3/20
Anti-HCV-IgM/HCV-RNA	4/20
Biliary obstruction (ultrasonography)	0/20
Alcoholism (AST/ALT ≥ 2)	0/20
Acute recent hypotension history (particularly if underlying heart disease)	0/20
Search for nondrug causes	
Group II	
Complications of underlying disease(s)	0/20
CMV (anti-CMV-IgM/PCR)	4/20
EBV (Anti-EBV-IgM/PCR)	3/20
HSV (Anti-HSV-IgM/PCR)	1/20

points). Certainly, the frequency of regulatory information regarding specified items required for causality evaluation was extremely low (Table 3).

It is of note that none of the kava independent causes (Table 1) was included in the CIOMS causality assessment (Table 2) since only those items were used which were reported by the regulator. Moreover, there was only little regulatory information regarding both the course of ALT after cessation of kava use and search for non-kava liver disease (Tables 2 and 3). Thus, problems of regulatory data communication, selection and deletion are evident. The aforementioned conditions precluded a structured causality assessment for kava.

3.4. Comparative evaluation

When various ad hoc causality assessments for kava in all 20 patients were compared with each other, little if any concordance is observed (Table 4). The problem of regulatory data presentation of low quality by BfArM (Tables 1–3) is perpetuated to the ad hoc assessments by MCA and EMEA, yielding mostly no or only low grades of causality (Table 4). Moreover, a probable and possible causality in one patient each and an unlikely or not assessable causality in the remaining 18 patients using regulatory and other additional data has been presented in another ad hoc study by Schmidt et al. (Table 4), and similar results were obtained in the present ad hoc causality study for kava (Tables 1 and 4).

The results of the present study with the updated structured CIOMS scores for kava (Table 2) were subsequently compared with those of a completed study using not only the regulatory data but also those by treating hospital physicians, primary care physicians, pharmacists, and drug companies (Table 4). There are higher grades of causality in the latter study compared to the former one (Table 4) with its low grade of regulatory data information (Tables 1–3). Regulators should therefore be encouraged to present a high grade of quality data when causality assessment is needed in suspected drug-induced liver disease.

Table 4
Comparative study of causality assessments for kava.

Patient	Ad hoc causality assessment					CIOMS causality assessment	
	BfArM	MCA	EMEA	Schmidt et al.	Present study	Present study	Completed study
1	Probable	Possible	Possible	Unlikely	Unassessable	Unlikely	Possible
2	Possible	Possible	Possible	Unlikely	Excluded	Unlikely	Excluded
3	Probable	Possible	Possible	Unlikely	Excluded	Unlikely	Excluded
4	Probable	Unlikely	Unlikely	Unlikely	Excluded	Unlikely	Excluded
5	Probable	Unassessable	Possible	Unlikely	Excluded	Excluded	Excluded
6	Probable	Possible	Possible	Unassessable	Unassessable	Unlikely	Unlikely
7	Probable	Unlikely	Possible	Unlikely	Excluded	Excluded	Excluded
8	Probable	Possible	Possible	Unlikely	Excluded	Excluded	Excluded
9	Certain	Probable	Probable	Unassessable	Unassessable	Excluded	Excluded
10	Certain	Probable	Probable	Unlikely	Unassessable	Excluded	Unlikely
11	Probable	Probable	Probable	Unassessable	Excluded	Unlikely	Excluded
12	Probable	Unassessable	Unassessable	Unassessable	Excluded	Possible	Probable
13	Probable	Unassessable	Unassessable	Unassessable	Unassessable	Unlikely	Possible
14	Possible	Unassessable	Unassessable	Unassessable	Unassessable	Excluded	Excluded
15	Probable	Unassessable	Unassessable	Unassessable	Excluded	Possible	Possible
16	Probable	Unassessable	Unassessable	Unlikely	Unassessable	Unlikely	Possible
17	Probable	Possible	Possible	Unlikely	Unassessable	Unlikely	Excluded
18	Possible	Unassessable	Unassessable	Unassessable	Excluded	Unlikely	Excluded
19	Certain	Probable	Probable	Probable	Highly probable	Unlikely	Highly probable
20	Probable	Possible	Possible	Possible	Possible	Unlikely	Probable

The results are shown for ad hoc causality assessments regarding kava in all 20 patients by various institutes including BfArM [4], MCA [16,24,33], EMEA [16,24,34], Schmidt et al. [16,24] and the present study (Table 1). The basis of these evaluations are the data presented and assessed by the Germany regulatory agency BfArM for kava [4]. The updated CIOMS causality assessment includes the present study (Table 2) and the data of the completed study [18,35], which used all data presented by the regulator, treating hospital physicians, primary care physicians, pharmacists, and drug companies and showed additional causality for co-medication being possible (cases 1 and 16) and probable (case 20) [18]. For details see Section 2.

4. Discussion

The national regulatory agency in Germany has attributed the causality of liver disease in the 20 patients due to treatment with ethanolic and acetonic kava extracts, and has classified them as: highly probable, probable, or possible based on an ad hoc evaluation [4]. However, the quality of the regulatory data presentation has been a matter of worldwide debate [5–19]. The present analysis shows major deficiencies in the regulatory data presentation regarding the individual cases (Tables 1–3). These are not substantiating the communicated regulatory causality assessment made on an ad hoc basis (Table 1); but instead, rendering an unrelated causality for kava in virtually all patients when the structured quantitative CIOMS scale was applied (Tables 2 and 4). It therefore appears that the regulatory causality strategy regarding assumed kava hepatotoxicity should be reassessed and officially revised.

Deficits of regulatory data presentation and subsequent causality assessment in cases with suspected kava hepatotoxicity are not limited to Germany as shown in the present study (Tables 1–4). They are also evident in regulatory agencies of various other countries [16,24,35]. These overall regulatory shortcomings regarding assumed kava hepatotoxicity are the basis of worldwide discussions [5–9,14,16,17,24,35].

There is general agreement that the diagnosis of toxic liver disease elicited by synthetic drugs, herbal remedies and dietary supplements is a major challenge [3,26,36–43], involving not only physicians but also drug companies and regulators [26]. Ad hoc causality assessment of toxic liver disease may be useful in the beginning of the causality evaluation process [26,29] but should be avoided later on in face of a broad spectrum of missed diagnosis [18,26], also found in the present study of the regulatory ad hoc causality assessment (Table 1). Moreover, the results of ad hoc causality assessment in identical patients vary substantially (Table 4), even between BfArM, MCA and EMEA, a situation not acceptable for any regulatory causality assessment.

Causality assessment of toxic liver disease is commonly performed using the structured quantitative score of the CIOMS scale which is based on various items [25,27] and has been recently updated [26]. Applying the scores of the updated CIOMS items in the

present study to the regulatory communicated data of 20 patients, causality for kava could be established in only 2 out of 20 patients (Tables 2 and 4) as a consequence of low quality and quantity of data presented by the regulator (Tables 1–3). Standard causality assessment should therefore include appropriate data supply for each patient and the use of the updated structured quantitative CIOMS scale.

To avoid problems of causality assessment regarding toxic liver disease, it is recommended that at first the reporting physicians uses, the updated quantitative CIOMS scales and submit these, item by item, to the respective national regulatory agency. The aim of this approach is not only to assure prompt and complete data presentation and verifiable causality assessment, but also to avoid unnecessary discussions as exemplified in the past for cases with assumed kava hepatotoxicity. In case that the data presentation and causality assessment by the reporting physician is a problem, the national regulatory agency will have to collect all relevant data of patients with suspected drug-induced liver disease, and submit the results to a causality assessment, such as the updated quantitative CIOMS score. All data including the causality assessment with point by point evaluation should then be made available to other regulatory agencies and the scientific community. At least in part, the usefulness of the application of the quantitative CIOMS scales was demonstrated only recently by EMEA for causality assessment in 42 patients with liver disease in assumed causal relationship to the treatment by black cohosh [2]. In only 4 out of 40 patients, causality was provided by EMEA without listing item by item. When the listing was completed, all four patients lost causality on various grounds [3]. The application of the updated CIOMS scale is therefore helpful, provided that item by item are being assessed.

In summary, the regulatory data presentation and ad hoc causality assessment of patients with liver disease in assumed relation to the treatment by kava extracts was insufficient. Reporting physicians and regulatory agencies are encouraged to collect all relevant data and to apply the updated structured quantitative CIOMS scale for causality assessment of assumed toxic liver disease in temporal association with the use of chemical drugs, herbal remedies and dietary supplements. For the cases of assumed kava hepatotoxicity,

the regulator should make public the details of all patients to the other regulatory agencies worldwide and the scientific community, and a reassessment of the regulatory causality assessment should follow.

Conflict of interest

None declared.

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