Supplementary management of functional, hepatic damage with Liverubin® (pharma-standard water soluble Silymarin): a 3-month registry

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Aim. **Mild, temporary hepatic failure (MTHF) is a common clinical problem; in case of repeated episodes MTHF may cause chronic liver impairment. This registry has evaluated MTHF in subjects using Liverubin® (standardized water soluble silymarin) for 8 weeks.**
Methods. **MTHF was evaluated in a registry study. In all subjects viral hepatitis markers were negative at inclusion. Different possible causes of MTHF had been considered. In these subjects alcohol was not a main factor. The registry included MTHF patients with decreased albumin levels, increased total bilirubin, altered hepatic function enzymes, increased oxidative stress. Two management groups were created: a standard management (SM) group and a SM+ Liverubin® group; 32 Liverubin® patients and 33 SM subjects completed the registry. Liverubin® was used at the dosage of three tablets daily.**
Results. **Distribution of symptoms, blood test values and ultrasound results were comparable. Symptoms observed at inclusion disappeared at 3 months in both groups. The increase in albumin levels was significantly (P<0.05 at 4 weeks) faster and the final blood tests improved more with Liverubin®. Total bilirubin was reduced with the supplement (better than in controls; P<0.05). Direct bilirubin values improved more in the supplement group at 3 months (P<0.05). The decrease of ALT-SGPT and AST-ASAT was more evident in the supplement group (P<0.05). Alkaline phosphatase value was normalized in Liverubin® patients; values decreased less in controls (P<0.05). GGT decreased more with Liverubin®. ESR was decreased in both groups (significantly more with Liverubin®: P<0.05). There was decrease in controls at 3 months. The white cell count was also better with the supplement group; P<0.05). Plasma free radicals — significantly elevated in both groups at inclusion — decreased more with the supplement at 3 months. All other blood tests (including hematocrit, renal function tests) were within the normal range at inclusion and at 3 months in both groups. Hepatitis markers were negative at inclusion and at end-registry. Safety and tolerability were optimal (no side effect was registered).**
Conclusion. **In conclusion, data from this pilot, registry study indicate a significant activity of Liverubin® associated with a very good safety profile, in patients with mild temporary hepatic failure. The recovery of hepatic function is faster and more effective with Liverubin® compared to the best "standard" management.**

KEY WORDS: Liver failure - Hepatitis - Silymarin - Jaundice - Bilirubin - MTHF - LFT'S.

Hepatic insufficiency may be caused by infective or non-infective causes including food, some drugs, alcohol or a combination of elements. Mild, temporary hepatic failure may be asymptomatic or cause minimal symp-

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toms.[1-7] This common problem may evolve into chronic liver impairment in a significant number of patients. Alcohol is possibly the most common cause of liver disease.[1, 2] It is directly toxic for hepatocytes and can cause a specific alcoholic hepatitis (AH). With chronic abuse, functional alterations may lead to cell necrosis, fat cell accumulation and severe organic changes. Drug-induced liver diseases also cause necrosis due to acute or chronic exposure.

Common drugs may cause damage after an excessive dose leading to liver injury [1, 7] but some drugs may cause damage even at appropriate dosages. The rate of hepatic complication following the use of medications is probably high; most episodes may be subclinical and undiagnosed.[1, 7] Methotrexate, used for autoimmune diseases and some tumors, may cause significant liver damage and chronic alterations leading. Disulfiram (antabuse) used to treat alcoholic addiction may be cause of liver failure.[4-6]

Hepatotoxicity is also associated with several anti-inflammatory compounds.[4-7]

The damage induced by drugs may be more evident when hepatic alterations — including alcohol or viral damages — are already present. Statins and niacin also cause liver damage even at appropriate dosages.[1, 2] Liver enzymes may be altered in most patients and are generally diagnostic. Several treatments, drugs and medications may cause liver impairment (*i.e.*, antibiotics: tetracyclines, nitrofurantoin, isoniazid, amoxicillin, clavulanic acid). Phyto-products and excessive amounts of vitamins may cause hepatitis, liver failure and cirrhosis (vitamin A, Kava-Kava, ma-huang, and comfrey). Some mushrooms are extremely, acutely poisonous even at low quantities for hepatic cells. The hepatic damage may kill in hours. In most patients the damaging agent or situation causing MTHF is not easily identified or may be hidden by the patients.

The management of MTHF [4-7] is based on avoiding the toxic or damaging agents and situations causing functional damage. Viral hepatitis should be always excluded in any patients with MTHF. At the moment, there is no defined standard of treatment. Avoiding further damage and metabolic stress is a key element in management. Hydration, diet, observation (repeating blood tests, particularly the enzymes associated with MTHF) define the supportive management modality. Some pharmacological agents have been used and are still used (including steroids). At the moment, however, there is no therapeutic standard. N-acetylcysteine may be effective in some cases of undefined, acute liver failure.[2-8] A recent study [8] has indicated a protective effect of a specific oak wood extract on liver injury. Liverubin® and silymarin have also been used in several clinical studies.[10-15] Liverubin® (Alchem) is a standardized water soluble formulation based on the synthesis from Milk Thistle seeds used in the management of liver damage. It has been extensively studied and used.[10-15]

The aim of this pilot registry was to evaluate the evolution of MTHF in subjects using Liverubin® for 3 months (3 tablets each equivalent to 140 mg of active ingredient daily).

Materials and methods

Inclusion criteria

Patients with MTHF were studied — after informed consent, in a registry study. In all registered subjects viral hepatitis markers were negative. Possible causes of MTHF had been evaluated (Table I), documented or excluded. Alcohol intake in these subjects was mainly associated with other factors not definitely determinant as a single factor is causing MTHF. The registry included patients with MTHF characterized by decreased albumin levels, increased total bilirubin, altered hepatic function enzymes and an increase in oxidative stress.

Management of acute mild-moderate liver failure

For these patients, the best management option is to avoid further negative effects of toxic agents. Patients must observe an adequate diet, rest and sleep, good hydration

also improving lifestyle (avoiding alcohol and any potential, damaging agents).

This open-label, registry included patients with a clinical and laboratory diagnosis of acute, moderate hepatic insufficiency based on enzymes and blood tests and on an evaluation of the liver with high-resolution ultrasound that excluded anatomic and organic lesions.

Exclusion criteria

The Body Mass Index (BMI) was <26; obese subjects were excluded. Patients were excluded in case of unstable, severe or rapidly progressing disease, renal disease and if they had history of hepatitis, if they were HIV-positive or had metabolic disorders requiring treatment (including anemia and diabetes). Congenital liver abnormalities, unstable mood and attention disorders, addictions, significant medical history requiring treatment, including the use of barbiturates or antiepileptic medications were also causes for exclusion.

Signs and symptoms

Minor, vague signs or symptoms were observed and were considered for inclusion in this registry (at least 3 symptoms were present in the weeks before inclusion) in association with laboratory alterations. Signs and symptoms variations were considered a secondary target (not all patients clearly show signs/symptoms). Tiredness, fatigue, change in urine color, malaise, nausea, vomiting, upper right quadrant tenderness or pain were variably present in the registry subjects. Ultrasound-documented mild, liver enlargement and mild splenomegaly were also present in all included subjects (Table I).

Liverubin® [9-14] was used at the dosage of three tablets (140 mg) daily.

Plasma free radicals

Oxidative stress in plasma was measured with a drop of blood in seconds, as validated in several studies.[16-18] This method evaluates reactive oxygen species in peripheral blood (measurements are expressed in Carr Units).[18]

All blood tests evaluated at inclusion and were repeated at 3 months.

Supplement studies

Supplement, registry studies [19] define the field of activity of supplements and possibly, preventive, preferably non-clinical applications. The best fields of application for supplements are preclinical, borderline applications or the supplementary management of risk conditions. Supplements unless there are specific claims are not generally used for treatment of signs/symptoms or clinical conditions. The aim of supplement studies is to produce supplementary data to be compared to "background" historical data (*i.e.*, based on the best available management for comparable subjects) or to other management plans. In this study the supplement was used according to the following rules:

1. The use of the supplement was suggested to the evaluation subjects; the supplement use was not prescribed but suggested as an option, possibly capable of improving the management of the risk condition.

2. The supplement was only used on top of what was considered the "standard"

TABLE I.—*Possible associated causes for moderate liver failure.*

Group	Liverubin® supplement group	Controls group - standard management (SM)
Number of subjects	32	33
Antibiotics	3	2
Combination with unknown drugs	3	3
Concomitant alcohol intake	8	7
Aspirin use	4	3
Anti-inflammatory drugs	7	8
Unknown	7	10

Viral hepatitis was excluded.

or best-management/care available, for that condition, according to international guidelines.

3. The use of the supplement should not have interfered with any other treatment, management or preventive measure.

4. Time: the period of follow-up was considered variable, according to the needs and availability of the patients or registry subjects. The observation period is therefore variable, not prefixed. Ideally, the supplement administration should be used as long as needed to see results or changes.

5. The type of evaluation for these studies is always a registry. The evaluation of the compliance concerning the use of the supplement is a significant value indicating how many subjects are actually willing to use the product. In these supplement studies there is no defined group allocation, no randomization organized by the investigators. Subjects decide on the basis of the initial briefing the management group they want to join including the control (non-supplement) group. No placebo is used.

Open label

Patients are always informed about the supplement or any treatment and management measure. A possible placebo effect is carefully explained and considered.

Data and results are analyzed only after the observation period, ideally, when sufficient evidence is collected or when fund limitations would eventually stop the collection of the observations. The time needed to detect differences among group is also considered an evaluation target. In this type of studies control groups, if present, are not necessarily parallel.

This study — extension to 3 months of a previous registry [20] — was a pilot, independent, registry study; the evaluation product was not prescribed but recommended. Commercial sponsorship from the producers of the tested supplement was not available.

Liverubin® [9-14] was used at the dosage of three tablets (each equivalent to 140 mg of active ingredient) daily.

Safety and tolerability

Safety and tolerability were assessed by clinical evaluation and laboratory measurements. Possible adverse experiences were monitored. Clinical adverse experiences were evaluated for intensity, considering duration, seriousness, outcome, and relationship to the study drug.

Statistical analysis

Sample sizes were determined (at least 20 subjects in each group) on the basis of a previous comparable study. Clinical and blood tests data were considered as non-parametric. An analysis of covariance (ANCOVA) model was used considering supplemented subjects *vs* controls using standard management with the corresponding 90% confidence intervals (CI).

Results

Table I indicates suspected causes of hepatic injuries detected from the medical history. In the final registry there were reliable informations concerning 32 Liverubin® patients and 33 comparable controls completing the full period (Table II). The average follow-up period was between 94;1.3 days in the supplement group and 99.3;2.3 days in controls.

Signs and symptoms

Table II shows the distribution of the most common symptoms and signs with ultrasound scans. The two groups (Liverubin® + best management and best management only) were comparable at inclusion. The beginning of the MTHF episode was difficult to associate to specific events (*i.e.*, drug administration or alcohol).

Symptoms in most patients were almost subclinical. Most symptoms observed at inclusion were completely disappeared or greatly attenuated after 6-8 weeks. The evaluation of these patients mainly relies upon blood tests, as symptoms are very subjective Table III shows the results of the blood tests (inclusion and at 3 months). The in-

TABLE II.—*Details of the two management registry groups (A). Drop-outs were due to missed controls.*

A.

Number Completing	Group Standard Management		Management	Lost/Drops*
32	Liverubin® (LR)	(age range 45-60; 26 males)	Best management + LR	0
33	Controls	(age range 45-61; 24 males)	Best management only	3

B.

Signs/symptoms at inclusion	32 LR subjects		33 controls	
	Inclusion	3 months	Inclusion	3 months
Tiredness	31/32	4/32*	28/33	6/33
Fatigue	30	4*	29	8
Change in urine color	29	2*	22	2
Malaise	29	4*	26	8
Nausea	18	0*	19	3
Vomiting	18	0*	18	0
INR (normal)	all	all	all	all
Upper right quadrant tenderness/pain	16	1*	17	3
Ultrasound-documented				
– Mild liver enlargement	26	11*	26	15
– Mild spenomegaly	10	3*	7	9

Number of patients with the symptom out of the total group.
*P<0.05 in comparison with controls.

crease in albumin was significantly (P<0.05 at 3 months) faster and the final values were higher with Liverubin®. Total bilirubin was reduced with the supplement group better than in controls (P<0.05). Direct bilirubin values improved more in the supplement at 3 months (P<0.05). The decrease in ALT-SGPT and AST-ASAT was greater with the supplement (P<0.05). Improvement in controls was more limited. Alkaline phosphatase was normalized at 3 months with Liverubin®. The test values decreased less in controls (P<0.05).

GGT decreased and were normalized at 3 months with the supplement. The ESR (erythrocite sedimentation rate) was decreased in both groups, more in the Liverubin® group (P<0.05). There was a more limited decrease in controls with persisting high values for weeks. The white cell count was also better at 3 months (with a larger decrease with the supplement; P<0.05).

Oxidative stress

Plasma free radicals (PFR) were elevated in both groups at inclusion. A more significant decrease in the supplement group was observed at 3 months. Persisting elevation in values were seen in controls (P<0.05 in comparison with normal range). Platelets values improved in the Liverubin® group (P<0.05) better than in controls. Other blood tests (including hematocrit, renal function tests) were within the normal range at inclusion and at 3 months in both groups. Hepatitis markers were also negative when repeated at 3 months in all subjects.

Compliance

The Liverubin® tablets were correctly used in 98% of patients. Safety was optimal and no side effects were registered. Tolerability was optimal; no patient had to stop treatment.

Discussion

Alterations in hepatic function are very common and challenging as they may be due to several, possible hepatotoxic causes. The often subclinical picture is confusing

TABLE III.—*Results at 1 and 3 months.*

					Results	
1. Albumin	3.5-5.3	g/dl	LR	3.13;1.1	4.5;1.1*#	5.2;1.1 *#
			CONTROLS	3.22;1	3.7;1*	4.1;1.1
2. TOTAL BIL	0.2-1.2	mg/dl	LR	2.7;0.8	1.33;0.6*#	1.1;0.5*#
			CONTROLS	2.72;0.7	1.9;0.6*	1.33;0.5
3. DIRECT BIL	0.1-0.4		LR	0.11;0.1	0.2;0.2*#	0.48;0.1*#
			CONTROLS	0.12;0.2	0.13;0.2*	0.29;0.1
4. ALT-SGPT	7-56	IU/L	LR	144;28	52;13*#	44;11*#
			CONTROLS	153;18	72;29*	55;13
5. AST-ASAT	5-47	IU/L	LR	143;23	51;11**	#44NS
			CONTROLS	154;26	82;16*	44;12
6. ALK PHOSPHATE (ALP)	30-120	IU/L	LR	184;27	118;14*	87;22*#
			CONTROLS	191;27	139;*#	142;31
7. GGT	0-42	IU/L	LR	119;22	44;15*#	36;12*#
			CONTROLS	128;21	66;16*	64;21
7. ESR	0-23	mm/h	LR	43.3;11	23.2;7*#	20.2;5.2*#
			CONTROLS	48.2;6	33;6*	34;6
8. White Cell Count			LR	12 146	7 754*#	5011;443*#
			CONTROLS	11 869	9 435*	6 563;549
9. PLATELETS			LR	123 223*	177 472*#	202 223*#
			CONTROLS	132 004	133 573*	149 362
10. Ox stress	<310		Carr Units LR	446;39	342;19*#	339;22*#
			CONTROLS	438;22	403;19*	398;22

* P<0.05 in comparison with previous value.
#= P<0.05: difference between groups at 4 weeks and 3 months.

and difficult to diagnose early in most patients. Previous studies [20, 21] indicated safety and efficacy of Liverubin®.

Repeated hepatic damage and the associated increase in oxidative stress may cause severe functional and organic liver damage that later may become evident and severe.

MTHF is diagnosed by the observation of altered enzymes.[22-28] GGT may be elevated even in minor, subclinical hepatic conditions. This test may identifying the cause of an isolated elevation in ALP (as GGT is raised in chronic alcohol toxicity).[29] Improvements in enzymes are considered an indication of improvement. These tests are effectively used to monitor MTHF after drug or alcohol toxicity. In this registry GGT (elevated at inclusion) were more significantly reduced with Liverubin® administration in comparison with the control management.

Silymarin extracts have protective effects on liver and hepatic injury in most cases of functional hepatic failure.[10-15]

Liverubin® is highly standardized and is particularly soluble in water; this improves its bioavailability (2-3 times higher in comparison with other silymarin preparations). The effects of silymarin (specifically Liverubin®) in MTHF are most probably the result of a significant, acute, hepatotropic anti-inflammatory action at hepatocytic level.[20, 21]

Pharma-standard supplements evaluated in open registries including the best present management versus the best management plus the supplement, are an important possible solution to evaluate new, possible management solutions to common clinical problems.

Conclusions

In conclusion, results of this pilot registry indicate and confirm a significant activity of Liverubin® associated with a very good safety profile, in hepatic failure. Recovery of hepatic function is faster and more effective with Liverubin®. The hepatoprotective

activities of Liverubin® may be mediated by its strong antioxidant activity in conditions of increased oxidative stress.

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