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A Preliminary Report on the Role of Liv.52 – An Indigenous Drug in Serum B Hepatitis (Australia Antigen Positive) Cases

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Patients with acute viral hepatitis have a severe course of illness, often characterised by anorexia, mild fever, hepatomegaly, splenomegaly, ascites and jaundice. These patients may die during the acute phase of the illness or chronic progressive liver disease may develop. Although the course of the disease is usually marked by distinctive clinical and laboratory abnormalities, the seriously ill patients may be more reliably identified by the finding of serum B hepatitis i.e. Australia antigen positive cases.

Several studies (Blumberg *et al,* 1965[1] Goeke and Kavey, 1969,[2] W.H.O. Technical Report, 1964[3] Ralph Wright *et al,* 1969[4] and Sama, 1977[5]) have reported the incidence of Australia-antigen positive cases in various liver disorders. The incidence reported from various parts of India varies from 0.5% (Prince, 1970[6] and Blumberg, 1970[7]). Blumberg *et al,* 1967[8] have shown that susceptibility to persistence of infection has an autosomal recessive triat. It is also dependent upon the immune response of the patients, which might determine the course of the disease. The management of this condition has remained unsatisfactory and no definite therapeutic agent is known which can eliminate the hepatitis-associated antigen.

Liv.52 (The Himalaya Drug Co.) an indigenous drug, is claimed to have a protective and regenerative effect on the hepatic parenchyma, to be a stomachic and a choleretic with a salutary effect on liver glycogen and serum proteins along with diuretic and anabolic actions (Patney *et al* 1974 and 1976)[9,10]. In view of these, it was considered worth while to investigate Liv.52 in the management of this crippling complication of Australia-antigen-positive associated serum hepatitis.

MATERIAL AND METHODS

Three hundred and forty patients with severe viral hepatitis (acute and chronic jaundice) were investigated for serum B hepatitis (Australia-antigen positive cases) by special counter-current electrophoretic technique and we were able to detect 20 cases of serum B-hepatitis. The incidence in this series was, therefore, 5.88%. These cases were admitted for observation in the medical ward of S.N. Medical College, Agra and were followed by personal contact.

A detailed history was taken and clinical examination was done. The following investigations were carried out in each case:

1. Counter-Current Electrophoresis for Australia-antigen testing[11].

2. Complete haemogram, which included haemoglobin levels, total, and differential count, erythrocytic sedimentation rate, general blood picture and red blood cell count.

3. Urine analysis for albumin, bile salts, bile pigments and urobilinogen.

4. Liver function tests consisting of serum bilirubin, serum proteins, albumin/globulin ratio, serum alkaline phosphatase. Van den Bergh reaction, thymol turbidity and flocculation, zinc sulphate turbidity.

5. Enzymatic tests consisting of glutamate oxalocetic transminase (GOT), glutamic pyruvic transaminase (GPT), lactate dehydrogenase (LDH) and isocitrate dehydrogenase (ICDH)[12].

6. Liver biopsy done by Van Silver man needle.

Out of these 20 cases, 6 were treated as a control group on regimen I i.e. (oral glucose, vitamins B and C, and steroid-prednisolone 5 mg t.i.d.) and the remaining 14 cases in the test group were put on regimen II i.e. (oral glucose, vitamins B and C, steroids along with Liv.52, 2 t.i.d.) for a period of 6 months. The haematological examination, urine analysis, liver function tests and enzymatic levels were repeated after every month of the therapy and Australia-antigen testing was repeated after every three months.

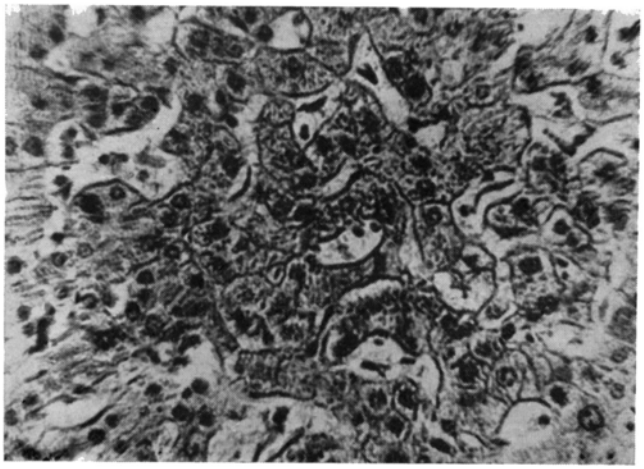

Figure 1.

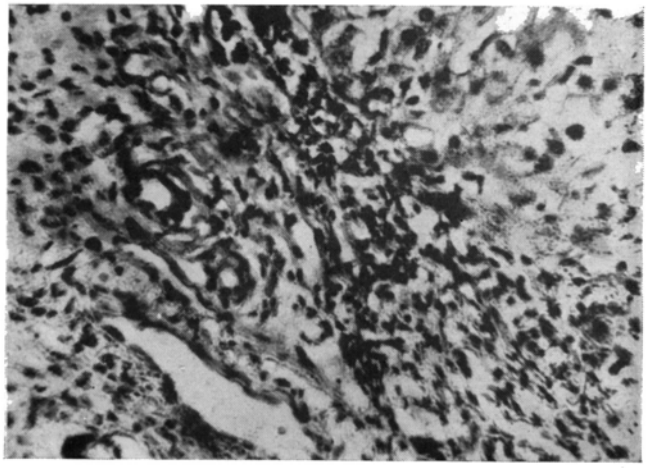

Figure 2.

Biopsies show the changes of condensation of portal tract involving fibrosis and mononuclear cell infiltration

OBSERVATIONS

Out of 20 cases of Australia-antigen positive, 18 were males and 2 females. Their age ranged from 25-40 years.

RESULTS

Liver Biopsy: In the Test group (14 cases), 10 biopsies were done. All showed the changes of condensation of portal tracts involving fibrosis and mononuclear cell infiltration (Figs. 1 and 2).

Haematological examination: This study showed that there was a significant improvement in haematological findings in the Test group (14 cases) receiving Liv.52 tablets along with steroids and other supportive treatments as compared to the Control group (6 cases) without Liv.52 as shown in Tables IA and IB. The rate of improvement in haemoglobin, TLC and ESR was better in the Test group in comparison with the Control group (Fig. 3).

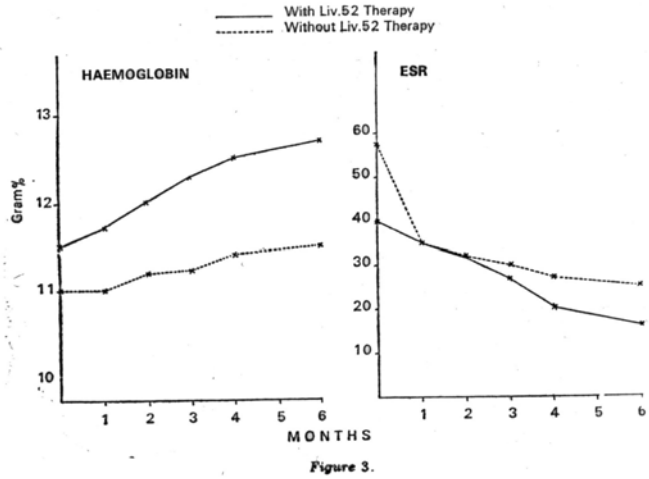

Figure 3.

Showing mean rise/fall in haematology before and after therapy

Urine examination: Patients in the Liv.52 group showed a rapid and progressive improvement in bile metabolism of the liver as compared to the Controls without Liv.52. In the patients of Liv.52 group, the amount of albumin, bile salts and bile pigments became less after one month of Liv.52 therapy and was absent after the 2nd month of therapy, as compared to the

Control group where they became less after the 2nd and 3rd month and were absent after six months' therapy. The amount of urobilinogen also showed a rapid improvement in the Test group within two months of Liv.52 therapy while in the Controls the amount of urobilinogen came from 1/50 to 1/40 after the 4th month of therapy.

Table 1A: Mean results of haematological examination in the Control group before and after receiving regimen I without Liv.52

Timings	Hb g%	TLC cells/mm	DLC			ESR mm fall 1st hr.
			P	L	E	
On admission	11.0 ± 2.14	9800	79	20	1	48
After 1st month	11.0 ± 2.00	9200	78	21	1	35
2nd month	11.2 ± 1.96	10000	82	17	–	32
3rd month	11.2 ± 2.96	11000	80	20	–	30
4th month	11.4 ± 2.30	11500	75	25	–	27
6th month	11.5 ± 1.93	12000	76	24	–	25

Table 1B: Mean results of haematological examination in the Test group before and after receiving regimen II with Liv.52

Timings	Hb g%	TLC cells/mm	DLC			ESR mm fall 1st hr.
			P	L	E	
On admission	11.5 ± 1.82	8500	80	19	1	40
After 1st month	11.7 ± 1.63	8300	75	25	–	35
2nd month	12.0 ± 2.06	8350	70	30	–	32
3rd month	12.3 ± 2.00	8400	65	35	–	27
4th month	12.5 ± 1.84	8300	70	30	–	27
6th month	12.8 ±1.68	8300	72	38	–	16

Table IIA: Mean results of urine analysis in the Control group before and after receiving regimen I without Liv.52

Timings	Albumin	Bile salts	Bile pigments	Urobilinogen
On admission	Traces	++	++	1/30
After 1st month	Traces	+=	++	1/30
2nd month	Traces	+	++	1/20
3rd month	Nil	+	+	1/20
4th month	Nil	Nil	+	1/10
6th month	Nil	Nil	Nil	1/10

Table IIB: Mean results of urine analysis in the Test group before and after receiving regimen II with Liv.52

Timings	Albumin	Bile salts	Bile pigments	Urobilinogen
On admission	++	++	++	1/40
After 1st month	Traces	+	+	1/20
2nd month	Nil	Nil	Nil	1/10
3rd month	Nil	Nil	Nil	Nil
4th month	Nil	Nil	Nil	Nil
6th month	Nil	Nil	Nil	Nil

Liver Function Tests: On surveying the mean results of liver function tests, a marked improvement was observed in the Test group on Liv.52 as compared to the Control group. There was a rapid fall in the serum bilirubin level and a rise in the levels of total serum proteins and serum albumin. Besides this, there was an early fall in the levels of serum globulin, zinc sulphate turbidity and serum alkaline phosphatase after Liv.52 therapy (Table III B). This clearly indicates that patients of the Test group showed a good response to Liv.52 therapy.

Table IIIA: Mean results of liver function tests in the Control group before and after regimen I without Liv.52									
Timings	Serum bilirubin mg%	Total serum protein g%	Albumin g%	Globulin g%	Van den Bergh reaction	T.T. units	T.F. units	Z.S.T. Units	Serum alkaline phosphatase K.A. Units
On admission	7.1 ± 2.06	6.8 ± 0.58	3.0 ± 0.53	3.8 ± 0.62	DI+	10	+2	16	46 ± 12
After 1st month	5.2 ±1.98	6.8 ± 0.93	3.2 ± 0.73	3.6 ± 0.59	DI+	6	+2	16	40 ± 16
2nd month	3.8 ± 1.62	6.9 ± 1.62	3.2 ±0.37	3.7 ± 0.69	DI+	6	+1	12	35 ± 10
3rd month	2.7 ± 1.90	6.9 ±1.03	3.3 ± 0.46	3.6 ± 0.38	DI+	4	+1	10	31 ± 13
4th month	1.8 ± 1.34	7.0 ± 0.86	3.4 ± 0.72	3.6 ± 0.63	DD+	3	Neg.	10	27 ± 9
6th month	1.6 ± 1.00	7.1 ± 0.63	3.5 ± 0.45	3.6 ± 0.81	Neg.	3	Neg.	8	18 ± 9

Table IIIB: Mean results of liver function tests in the Test group before and after regimen II with Liv.52									
Timings	Serum bilirubin mg%	Total serum protein g%	Albumin g%	Globulin g%	Van den Bergh reaction	T.T. units	T.F. units	Z.S.T. Units	Serum alkaline phosphatase K.A. Units
On admission	11.0 ± 3.0	6.9 ± 1.14	2.9 ± 0.47	4.0 ± 0.26	DI+	8	+2	15	52 ± 18
After 1st month	7.0 ±2.6	7.0 ± 1.60	3.0 ± 0.73	4.0 ± 0.18	DI+	6	+1	10	43 ± 15
2nd month	4.0 ± 1.8	7.1 ± 1.03	3.3 ± 0.81	3.8 ± 0.43	DD+	4	+1	8	38 ±10
3rd month	2.9 ± 1.7	7.2 ± 1.01	3.5 ± 0.62	3.7 ± 0.72	DD+	3	Neg.	7	29 ± 12
4th month	1.0 ± 0.3	7.3 ± 0.92	3.8 ± 0.58	3.5 ± 0.52	Neg.	2	Neg.	7	20 ± 8
6th month	0.9 ± 0.3	7.5 ± 0.82	4.0 ± 0.41	3.5 ± 0.35	Neg.	2	Neg.	5	14 ± 6

On the other hand, the Control group showed some improvement in liver function test after a long period of steroid and other supportive treatment. There was a fall in the serum bilirubin levels and a rise in the total serum proteins, serum albumin and very slight change in serum globulin level. There was also a fall in zinc sulphate turbidity and serum alkaline phosphatase. The improvements however, were not to the same extent as seen in the Liv.52 group (Figs. 4 and 5).

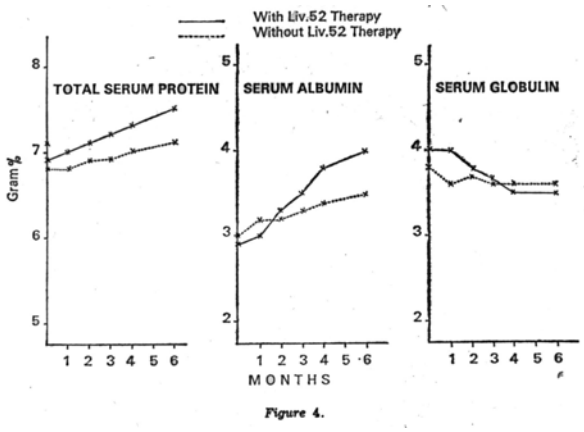

Figure 4.

Showing mean rise fall in serum protein albumin and globulin ratios

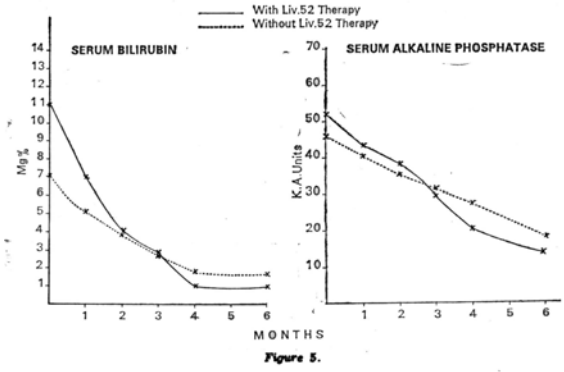

Figure 5.

Showing mean fall in serum bilirubin and alkaline phosphatase

Enzymatic tests: There was very good improvement in the Test group on Liv.52 showing a rapid decrease in the enzymatic levels. There was a rapid fall in SGOT, LDH and ICDH (Table IV B).

Table IVA: Mean results of serum enzymatic studies in the Control group before and after regimen I without Liv.52				
Timings	SGOT IU/L	SGPT IU/L	LDH IU/L	ICDH IU/L
On admission	55.10 ± 30.0	121 ± 52.6	700 ±240	81.25 ± 32.0
After 1st month	50.00 ± 22.6	108 ± 30.8	610 ± 138	70.00 ± 42.6

2nd month	42.00 ± 20.9	64 ± 20.3	530 ± 140	58.00 ± 35.0
3rd month	35.00 ± 16.2	48 ± 15.1	460 ± 98	45.00 ± 23.6
4th month	22.00 ± 10.8	30 ±14.7	400 ± 167	37.00 ± 17.8
6th month	18.00 ± 6.3	22 ±13.6	340 ± 60	28.00 ± 13.0

Table IVB: Mean results of serum enzymatic studies in the Test group before and after regimen II with Liv.52

Timings	SGOT IU/L	SGPT IU/L	LDH IU/L	ICDH IU/L
On admission	62.70 ± 20.12	139.6 ± 40.8	760 ± 230	109 ± 38.0
After 1st month	57.20 ± 22.8	116.4 ± 62.3	475 ±117	52 ±17.9
2nd month	34.60 ± 17.3	47.8 ±19.2	320 ± 163	30 ±10.8
3rd month	17.5 ± 10.0	18.9 ± 6.2	260 ± 64	16 ±6.7
4th month	16.0 ± 5.9	18.0 ± 8.4	260 ± 93	14 ± 4.3
6th month	14.0 ± 4.6	17.0 ± 10.0	265 ± 85	13 ± 2.0

The Control group also showed some improvement in enzymatic levels after a long period of steroid therapy, but this improvement was very slow in comparison with the Liv.52 group (Fig.6).

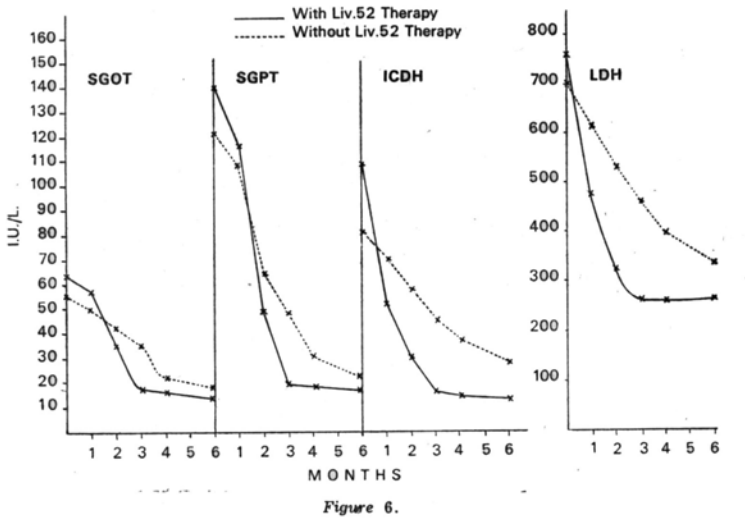

Figure 6.
Showing mean rise/fall in enzymatic levels before and after therapy

DISCUSSION

From the numerous studies on the prevalence of hepatitis B surface antigen, it can be estimated that between 15 to 20 millions of the world's populations are infected with hepatitis B virus at any time. Prospective studies of these individuals indicate that most patients are chronically infected and exist either as so called inapparent HBsAg carriers or as patients with chronic hepatitis. Until now, treatment of the chronically – infected individuals has been relatively disappointing. Current treatment recommendations apply only to patients with clinical hepatitis and are based upon the use of steroids and antimetabolites that suppress the immune response of the patients[13-16]. However, such therapy treats the host instead of the infection. Furthermore, immuno-suppression is believed to aggravate the symptoms of chronicity when administered before or during acute type-B hepatitis,[17] and mild chronic type B hepatitis in immunosuppressed patients has been reported to become much more severe after cessation of immunosuppression therapy[18]. The use of steroids on a long-term basis in the treatment of this condition exposes the patients to their well-known hazards. A preliminary impression of the beneficial effect of Liv.52 therapy in this condition prompted this study to test the utility of Liv.52 in chronic type-B hepatitis.

Two groups of patients, one consisting of 6 patients and the second of 14 patients were treated on regimen I i.e. oral glucose, vitamins B and C and steroid-Prednisolone 5 mg t.i.d. and regimen II, i.e. oral glucose, vitamins B and C, steroid along with Liv.52 x 2 t.i.d. respectively. The patients were carefully followed up over subsequent months for clinical and biochemical parameters and Australia-antigen testing every three months. The cases were followed up for a period of 6 months. The haemotological response to regimen II was on an average better than to regimen I. Bile pigments and salts also disappeared earlier in the Test group. Serum bilirubin did not come to normal in every case and averaged at 1.6 mg% by six months in the Controls but it dropped to

normal in the Liv.52 group. The anabolic activity of Liv.52 resulted in a better serum albumin concentration at the end of 6 months.

Study of serum flocculation test and various serum glycolytic enzymes including SGOT, SGPT, LDH and ICDH proved further beneficial effect of Liv.52 in chronic B-hepatitis. Elevation of SGPT as compared to SGOT in these cases indicated significant progressive liver fibrosis in these cases and although both SGOT and SGPT showed significant fall on both regimens, there was a persistently low level of SGPT as compared to SGOT even at the end of 6 months. Evidently these cases were caught late in the disease. Although the progress of fibrosis was retarded, it was by no means completely arrested. Obviously, the sooner these cases are detected and treated on these lines the better would be the long-term prognosis.

The beneficial roles of Liv.52 requires further confirmation with a greater number of patients and longer follow up. How Liv.52 works in these cases is not clearly understood. Both endogenous and exogenous interferons are reportedly effective in modifying chronic Hepatitis-B virus infection. Hill *et al,*[19] have reported the absence of detectable interferon in serial serum samples from patients with type-B hepatitis. Tolentino *et al*,[20] reported a decreased interferon response in lymphocytes from children with chronic type-B hepatitis and postulated that decreased production of interferon may be responsible for the chronicity of the disease. In contrast to the poor interferon inducing capacity of Hepatitis-B virus, Greenburg *et al,*[21] indicate that this virus is very sensitive to interferon.

Relatively low doses of interferon were apparently capable of markedly suppressing virus synthesis. Recently it has been shown that chimpanzee, chronically infected with hepatitis-B virus showed transient changes in several markers of infection, when treated with interferon inducer polyriboinosinic polyribocytidylic acid-poly-1-lysine carboxy-methyl cellulose (PICLC). Unfortunately, exogenous interferon is associated with toxic manifestations. It is difficult to prepare in large quantities and very expensive at present for induction of endogenous interferon. PICLC is the most promising inducer at present. This substance is relatively inexpensive but associated with toxic manifestation like bone marrow depression and is more difficult to administer – and is potentially immuno-reactive. More extensive studies are therefore needed before it is employed in the treatment of type-B hepatitis. Whereas Liv.52 is not only inexpensive, but has not shown any significant side effect so far in our experience. Liv.52 thus deserves a place in the maintenance therapy of this condition as it may help to control the progress of type-B hepatitis to chronic aggressive hepatitis along with minimal doses of steroids, thereby preventing long term toxic effects.

SUMMARY

Three hundred and forty patients with severe viral hepatitis (acute and chronic jaundice) were investigated for hepatitis associated with antigen. 20 cases of serum B hepatitis were detected, giving an incidence at 5.8 per cent. A review of literature showed that the management of this condition has remained unsatisfactory and no definite therapeutic agent is known, which can eliminate the hepatitis-associated antigen.

Liv.52 in view of its anabolic, choleretic and stimulatory action on the regeneration of hepatic parenchyma was taken up for trial in the management of serum B hepatitis. Six cases out of 20 were treated as Control group with steroids and supportive treatment. The remaining 14 cases were treated as Test group with Liv.52 along with steroids and supportive therapy for a period of 6 months. All the patients were examined clinically and biochemically every month during and after the scheduled therapy.

On comparing the results in both the therapeutic groups wee found an earlier and better recovery in the haematological picture, i.e. rise in haemoglobin (11.5 ± 1.82 to 12.8 ± 1.668g%) and a quick

fall in ESR (40 to 16 Wintrob) in the Test group. Though the Control group also showed improvement in haemoglobin (11 ± 2.14 to 11.5 ± 1.93g%) and ESR (48 to 25 Wintrob), this was very slow as compared to the Test (Liv.52 group).

Similarly, urine analysis showed that the bile salt and pigment diminished earlier after Liv.52 therapy in the Test group. While in the Control group these bile pigments disappeared after prolonged therapy.

A significantly early response to Liv.52 was observed in liver function tests i.e. (fall in serum bilirubin 11 ± 3 to 0.9 ± 0.3 mg%, serum albumin 2.9 ± 0.47 to 4.0 ± 0.41 g%) in the Test group as compared to the Control group (i.e. Hb. 7.1 ± 2.0 to 1.6 ± 1.0 mg%, and serum albumin 3 ± 0.5 to 3.5 ± 0.4 g%). In the Liv.52 group, serum enzyme levels came down after the first month of therapy and became normal after the third month i.e. SGOT 62.0 ± 20.0 to 14 ± 4.6 IU/L, SGPT 139 ± 40 to 17 ± 10 IU/L, LDH 760 ± 230 to 265 ± 84 and ICDH 109 ± 38 to 13 ± 2 IU/L. While the Control group also showed improvement, these levels came to normal only after the 5th and 6th month of steroid therapy.

Liv.52 can safely be used even in high doses and for prolonged duration without any hazards and side effects in the maintenance therapy of serum B hepatitis.

CONCLUSION

Thus we conclude that Liv.52 deserves a place in the maintenance therapy of serum B hepatitis (without any side effect) and may help to control the progress of type-B hepatitis to chronic aggressive hepatitis, along with the minimal dose of steroids thereby preventing long-term toxic effects.

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