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Prospectives on the treatment of chronic hepatitis B and chronic hepatitis C with thymic peptides and antiviral agents

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Abstract

At the present time, interferon is considered the only effective therapeutic approach in the treatment of both chronic hepatitis B and chronic hepatitis C. It is clear that the disappointing response rates in both chronic hepatitis B and C place added emphasis on efforts to identify alternative forms of therapy. In addition to the development of other antiviral agents including the nucleoside analogs which might prove more effective and have fewer associated side-effects, other agents currently under investigation include thymic peptides such as thymosin alpha 1. In the future, the therapeutic approach to the treatment of chronic hepatitis B and C may consist of combination therapy using perhaps an immune modulator and an antiviral agent or, several antiviral drugs. Alternatively, there is indication that cellular targeting systems with delivery of the toxic material to the specific cell containing the virus may be more effective, while minimizing side-effects. Finally, there are agents such as ursodeoxycholic acid which perhaps, makes bile less toxic and can be used as adjuntive therapy with improvement in liver chemistry values. The treatment of chronic hepatitis B and chronic hepatitis C has shifted in emphasis form the concept of treating liver disease towards that of treating viral infections which happen to effect primarily the liver.

Key words: Hepatitis B; Hepatitis C; Thymic peptide; Antiviral agent; Interferon

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1. Introduction

Interferon (IFN) therapy is currently the mainstay for the treatment of chronic viral hepatitis B and C. However, the response rates are still disappointingly low, and reactivation, once therapy is discontinued, is appreciable. Furthermore, side effects, though generally tolerable, are frequent. There is the need to develop other more successful drugs and strategies. Agents to be used alone or in combination with IFN or other drugs are actively being pursued. Although IFN has both antiviral and immuno-modulatory activity, investigations of other immune modifying agents as well as other antiviral chemotherapies appear to offer some hope of success. Other novel treatments or targeting and delivery systems are also being studied. This review will focus on some of these agents in the treatment of chronic hepatitis B and C. A number of other recent reviews provide good overview of agents previously or currently being studied for antiviral effect in chronic hepatitis (Perrillo, 1992; Hoofnagle et al., 1993; Mason, 1993; Perrillo, 1993).

1.1. Thymic peptides

Thymic factors are characterized as immune modifiers exerting influence on a variety of cellular and humoral immune responses both in vitro and in vivo. Thymic extracts and thymus-derived peptides have been evaluated in the treatment of chronic hepatitis B (CHB) and to a lesser extent, in chronic hepatitis C (CHC). The rationale for applying thymic peptide therapy in CHB is predicated on observations suggesting that there may be an impairment of the host cellular immune response in clearing hepatitis B virus (HBV) infected hepatocytes (Thomas, 1990; Katkov and Dienstag, 1991; Milich, 1991). With thymic peptide treatment it is believed that restoration of immune competence, as it relates to the host HBV interaction, would result in elimination of the HBV and termination of the progressive hepatic injury associated with the inflammatory process.

A thymic extract, termed TFX, was used to treat patients with CHB. In vivo improvements in T cell-mediated immune reactivity were observed in association with clinical improvements as determined by normalization of serum aminotransferase levels, resolution of hepatic inflammatory infiltrates and decreased HBV markers (Dabrowski et al., 1980). Unfortunately, the authors did not provide sufficient information to assess treatment efficacy. Sheng (1983) using a porcine thymic extract, treated patients with CHB displaying varying degrees of disease severity for periods ranging from 3 to 6 months. He achieved disease remission in 16 of 24 (67%) treated patients and observed spontaneous remission in 4 of 24 (17%) control patients. Histologic confirmation of CHB was not obtained prior to the treatment phase precluding accurate interpretation of the results. Furthermore, disease remission was based upon improvement in aminotransferase values and not on serum HBV DNA or HBeAg status.

Initial promising results of treatment response to thymopeptide (Zhang et al., 1986) and thymostimulin, an extract of calf thymus (Romeo et al., 1987), have been reported. However, although clinical, biochemical and histological improvements were seen in these studies, treatment effect on HBV DNA was not reported.

1.2. The thymosins

Thymosin fraction 5 (TF5) is a partially purified extract of bovine thymus containing more than 50 peptide components, 20 of which have been purified to homogeneity or near homogeneity (Low and Goldstein, 1984). A number of the peptide constituents in TF5, including thymosin α_1 ($T\alpha_1$), have been sequenced and synthesized (Wetzel et al., 1980). $T\alpha_1$ appears to represent the key biologically active component of TF5 and is highly conserved between mammalian species. Both TF5 and $T\alpha_1$ are potent inducers of T cells and can influence immunoregulatory function (Mutchnick et al., 1982; Sztein et al., 1986; Serrate et al., 1987; Baxevanis et al., 1987; Svedersky et al., 1982).

$T\alpha_1$ is an acidic 28 amino acid peptide (mw 3108) which has been measured in sera of healthy human subjects (Weller et al., 1992) as well as in patients with CHB (Sherman et al., 1991). $T\alpha_1$ has been shown to promote IFN-α, IFN-γ, and sIL-2 production by human lymphocytes and to increase IL-2 receptor expression (Sztein et al., 1986; Serrate et al., 1987; Baxevanis et al., 1987; Svedersky et al., 1982). In previous in vitro studies, TF5-treated peripheral blood mononuclear cells (PBM) from patients with CHB exhibited decreased spontaneous cell-mediated cellular cytotoxicity against rat hepatocyte monolayer cultures. PBM from healthy controls similarly treated with TF5 showed no change from background cytotoxic activity seen with non-treated PBM (Mutchnick et al., 1980). Furthermore, TF5 increased concanavalin A-induced suppressor T cell function in PBM from patients with CHB, but decreased suppressor function in PBM from healthy controls (Mutchnick et al., 1983).

TF5 was administered to 4 chronic HBsAg(+), HBeAg(+) chimpanzees for a period of 10–14 weeks. Two of the animals were pretreated for 4 weeks with corticosteroid. No significant effect was observed on disease status in the presence or absence of pretreatment corticosteroids (Eichberg et al., 1987). The TF5 was given intramuscularly following a loading dose (60 mg daily for 2 weeks) maintenance dose (60 mg, three times weekly) schedule. Subsequent experience has shown that thymosin is more successfully administered by subcutaneous injection and that the treatment period required is at least 6 months.

Synthetic $T\alpha_1$ was used to treat eastern woodchucks naturally infected with the woodchuck hepatitis virus (WHV), a member of the hepadnavirus family and closely related to HBV (Gerin et al., 1992). These animals, all displaying histologic evidence of chronic hepatitis, received 10 μg/kg body weight $T\alpha_1$ subcutaneously, twice weekly for 30 weeks. During the treatment and follow up period (to 1 year), untreated chronic WHV-infected animals showed no significant changes in both serum and liver tissue WHV DNA. $T\alpha_1$ treated woodchucks experienced a steady decrease in serum WHV DNA which was accompanied by a decline in replicative WHV forms in liver tissue. During the nearly 6 months post-treatment period, serum and liver tissue WHV levels returned to pretreatment values in surviving animals. No obvious drug-associated toxicity was seen.

Clinical trials in humans using $T\alpha_1$ as primary or adjunctive therapy indicate that the peptide enhances immune responsiveness and augments specific lymphocyte function in patients with immunodeficiency or cancer (Sztein and Goldstein, 1986).

Furthermore, $T\alpha_1$ appears to reconstitute immune defects rather than nonspecifically augmenting relatively normal immune parameters to significantly higher levels.

1.3. Thymosin treatment of chronic hepatitis B

We have previously reported on the results of a randomized, double-blind and placebo-controlled Phase II study designed to assess the safety and efficacy of several dosages of TF5 and $T\alpha_1$ in the treatment of CHB (Mutchnick et al., 1991; Mutchnick et al., 1992a). In this three arm study 12 patients received one of two dose concentrations of TF5 (90 or 120 mg/M^2 body surface area) or $T\alpha_1$ (900 μg or 1200 $\mu g/M^2$) by subcutaneous injections, twice-weekly, for 26 weeks and were followed for an additional 26 weeks post-treatment. Eight patients were randomized to receive placebo injections (1.4% sodium bicarbonate). All patients were HBsAg(+) and exhibited elevations in serum alanine aminotransferase (ALT) levels for at least 6 months. All tested positive for serum HBV DNA (dot blot) and had histologic confirmation of chronic hepatitis within 3 months of randomization. Four patients randomized to receive TF5 experienced discomfort at the injection sites during the first 2 weeks and, per protocol, were switched to $T\alpha_1$, for the ensuing 24 or 25 weeks. Response to treatment was defined as loss of serum HBV DNA (dot blot) and normalization or near normalization of the ALT values. Treatment effect on HBeAg was also monitored when present at inclusion into the study.

At the conclusion of the 1 year study, 9 of 12 (75%) thymosin-treated patients responded to treatment as compared to 2 of 8 (25%) patients given placebo and who experienced spontaneous remission of disease. Clearance rates for HBV DNA, HBeAg and HBsAg at 1 year are shown in Table 1.

Pretreatment and 1 year liver biopsy specimens were available on seven thymosin treated patients (six of whom were responders) and five patients given placebo (including 1 patient with a spontaneous remission). Replicative forms of HBV DNA were found in all 12 patients prior to treatment. At 1 year, the single patient given thymosin who did not show a response to treatment, still had replicative HBV molecular forms in the liver. Four thymosin treated patients had no replicative forms and the final two patients were found to have free genome forms presumed to represent a transition to a latent form of infection. Four of the five patients given

Table 1
HBV marker seropositivity at inclusion and at 12 months

HBV Marker		Thymosin-Treated (12)	Placebo (8)	*P* value
DNA	Initial	12 (100%)	8 (100%)	NS
	12 Months	3 (25%)	6 (75%)	<0.04[a]
HBeAg	Initial	11 (92%)	5 (63%)	NS
	12 Months	5 (42%)	4 (50%)	NS
HBsAg	Initial	12 (100%)	8 (100%)	NS
	12 Months	10 (83%)	8 (100%)	NS

[a]Fisher's exact test.

placebo still had replicative forms in the liver and the fifth patient, who demonstrated spontaneous remission of disease, had no replicative forms. Histologic improvement was observed between pre-treatment and 1 year liver biopsy specimens in the thymosin group but not in the placebo group (Mutchnick et al., 1991).

The nine patients who responded to thymosin have been followed for 2–5 years (3.5 ± 0.3 years) after completion of the injections (Mutchnick et al., 1992b). Two of the nine responders demonstrated recurrent serum HBV DNA and HBeAg with associated ALT elevations at 23 and 35 months follow up, respectively. Seven (78%) of the responders have experienced a sustained remission as characterized by normal ALT values and negative serum HBV DNA and HBeAg. Serum HBV DNA measurements were accomplished by the Abbott RIA HBV DNA assay. Additionally, these seven responders tested negative for HBV DNA using a PCR method sensitive at the 10^{-15} to 10^{-16} gm level. A more sensitive PCR methodology, capable of detecting HBV DNA at the $3\text{–}5 \times 10^{-18}$ gm level revealed that one of the seven responders was negative, four were trace positive and two were 1+ or 2+ positive. Nonetheless, five of these seven patients had seroconverted to a HBsAg(−), anti-HBs(+) status (Table 2). Thus of 12 patients treated with thymosin, 7 (58%) have experienced a sustained response to treatment suggesting a therapeutic efficacy in the treatment of CHB. Furthermore, no significant drug reactions to $T\alpha_1$ were observed.

$T\alpha_1$ has seen application in several additional studies in patients with CHB. In one study, six of seven patients with anti-HBe(+) CHB given $T\alpha_1$ demonstrated a response to therapy (Rezakovic et al., 1992). Results of a large Phase III multicenter Italian study evaluating the efficacy of $T\alpha_1$ as a single therapy are expected soon on patients with anti-HBe(+) CHB. In the United States, a Phase III multicenter trial using $T\alpha_1$ or placebo in patients with HBeAg(+) CHB will conclude in April, 1994. Other investigators have treated patients with CHB using combination therapy with $T\alpha_1$ and IFN. Most patients entered into this study had previously failed therapy with IFN alone. In this open label study, 14 of 15 patients tested negative for serum HBV DNA at the conclusion of the injections and the response rate at 6 months follow up exceeded 50% (E. Garaci, unpublished results).

Table 2
Characteristics of thymosin responders at last assessment

Patient	Follow up (mos)	ALT* (IU/ml)	HBsAg	Anti HBs	HBeAg	Anti HBe
1	60	14	–	+	–	–
2	54	30	–	+	–	(+)
3	56	7	–	+	–	ND
4	45	11	–	+	–	–
5	31	17	–	+	–	–
6	60	33	+	–	–	+
7	49	25	+	–	–	–
8	23	289	+	ND	+	ND
9	35	115	+	–	+	–

*Normal ALT < 50 IU/L.

Trials of combination therapy using $T\alpha_1$ and IFN or IFN alone in the treatment of chronic hepatitis C are ongoing (Sherman et al., 1993). A pilot study assessing the effect of $T\alpha_1$ as single therapy in chronic hepatitis C did not appear to show treatment benefit (Rezakovic et al., 1993).

The precise mechanism(s) by which thymosin mediates its effect in CHB and perhaps in chronic hepatitis C is unknown. There is evidence to suggest that in addition to its known immunomodulatory effect, $T\alpha_1$ may mediate its activity in a manner similar to IFN-α. The C-terminal sequence of IFN-α shares homology (36%) with prothymosin α, the precursor of $T\alpha_1$ (Zav'yalov et al., 1989). The C-terminal domain of IFN-α may be responsible for immunomodulatory activity.

The use of immunomodulatory thymic peptides in the treatment of CHB and, perhaps in chronic hepatitis C, represents an innovative approach, which differs from previous efforts which were directed towards anti-viral therapies.

1.4. Other immunomodulators

Like thymic peptides, isoprinosine (2-hydroxypropyldimethylammonium 4-acetomidobenzoate, 1:3) appears to have antiviral as well as immune-modulating effects. It has been less extensively investigated, however. Positive results have been reported in hepatitis B (Cianciara, 1990), but the drug is ineffective in hepatitis C (Laskus, 1992).

1.5. Other antiviral therapies

In addition to immunomodulatory agents in the treatment of chronic viral hepatitis, the major thrust in chemotherapy has been directed toward antiviral agents. Several of these agents have been available for some time and have been tested and approved for treatment of various other viral illnesses. Their ability to decrease viral replication would be viewed as an ideal characteristic to be exploited in illnesses such as CHB and CHC where decreased viral replication is associated with diminished clinical disease activity and, in some cases, cure. Antiviral agents have also been tested in combination with immunomodulator strategies to improve the rate of favorable response in CHB. Antiviral agents have been studied in animal models of viral hepatitis (Kassianedes et al., 1989; Ponzetto et al., 1991; Gerin et al., 1992) and in cellular systems (Korba and Gerin, 1992; Lampertico et al., 1991). The experience with these agents is far greater with CHB than CHC, since the availability of markers to accurately diagnose and follow HCV infection and HCV viral replication is relatively new.

The HIV epidemic has accelerated the process of examining antiviral agents in human patients. Many patients with HIV infection also are chronically infected with HBV and HCV, so the ability to study the effects on HBV viral replication, in particular, in patients with HIV being treated with antiviral agents has resulted in important clinical information. Moreover, HBV replication requires reverse transcriptase activity. Therefore, drugs being used to treat HIV infection by inhibition of reverse transcriptase activity could well have activity against HBV (Gerin, 1991).

1.6. Nucleoside analogs

To date, the class of antiviral agents most actively studied have been the nucleoside analogs. These agents inhibit viral replication by interfering with DNA and RNA synthesis by various mechanisms, especially the inhibition of viral polymerases. Unfortunately, these agents have similar effects on human cells and toxicity of many of these agents has been significant. In some instances viral resistance has developed.

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a non-interferon-inducing purine nucleoside analog that inhibits replication of many viruses. The drug is given orally. Effects of this agent in CHB were negligible although decreases in serum level of HBV DNA were noted in one study (Fried et al., 1992). Ribavirin has been used in several randomized trials in CHC patients (Kakumu et al., 1993A; Kakumu et al., 1993B; DiBisceglie et al., 1993; Reichard et al., 1991). Positive short term effects were reported for CHC, and the drug was well tolerated. However, enzyme levels in CHC patients rose with cessation of therapy, and eradication of hepatitis C viral RNA was infrequent. Trials in patients resistent to interferon (Brillanti et al., 1993) and immunosuppressed patients (Rezieg et al., 1993) indicated the agent may be useful in these clinical situations.

Vidarabine (arabinofuranosyladenine monophosphate) has demonstrated selective inhibition of hepatitis B replication during active treatment (Hoofnagle et al., 1984; Weller et al., 1985; Marcellin et al., 1989a). Results of treatment have been transient. This synthetic purine nucleoside analog is given intramuscularly. Significant muscular, neural and other toxicities are reported. Special applications when short-term suppression of hepatitis B replication might be indicated are reported for polyarteritis associated with hepatitis B (Guillevin et al., 1993) and for immunosuppressed patients after renal transplant (Pol et al., 1993).

Acyclovir (1–2′deoxy-2′-fluoro-β-D-arabinofuranosyl-5-iodocytosine) which is effective in the treatment of herpes viruses appears to be ineffective in the treatment of CHB (Alexander et al., 1987). 6-Deoxyacyclovir, though well absorbed, is no more effective (Weller et al., 1986). Acyclovir also appears to be ineffective in chronic non-A, non-B hepatitis/CHC (Pappas et al., 1986).

Fialuridine (1–2′ deoxy-2′ fluoro-1-β-D-arabinofuranosyl-5-iodouracil, FIAU), is a fluorinated nucleoside metabolite of FIAC (1–2′-deoxy-2′-fluoro-1-β-D-arabinofuronosyl-5-iodocytosine). FIAC was studied in CMV infection, where it was ineffective, but the drug, which is rapidly converted to FIAU showed activity against hepatitis B (Chikami et al., 1993). FIAU inhibits viral DNA or RNA polymerases by incorporating into the viral nucleotide chain as an analog of thymidine. In a 14 day dose de-escalating study of 20 HIV patients with CHB with measurable HBV DNA and HBeAg (Paar et al., 1992), there was marked and rapid suppression of HBV DNA. There was associated ALT elevation in several patients some with disappearance of HBV DNA and HBeAg. In other patients HBV DNA returned to significant levels when the drug was discontinued. The drug was generally well tolerated, thus prompting a 28 day study in non-HIV immunocompetent patients with CHB. 24 Patients entered this study and completed the regimen. Serum HBV DNA levels decreased markedly in all patients and continued to fall throughout the

study. ALT levels generally increased at the end of the treatment period. Disappearance of HBeAg was not seen, however (Fried et al., 1992).

Encouraged by these results, 24 patients were to be randomized to FIAU at doses of either 0.1 or 0.25 mg/kg per day for 24 weeks. Fifteen patients were enrolled. Of 10 patients who were treated for more than 4 weeks, 6 became negative for HBV DNA and the others showed significant inhibition of HBV. Therapy was stopped and the trial abruptly terminated, however, when 2 patients developed severe liver disease. Of the 10 patients treated for more than 4 weeks, 7 had developed severe toxicity and 3 mild toxicity. Toxicities included liver failure, lactic acidosis, pancreatitis, myopathy and neuropathy. Five of the 7 severely toxic patients died, 3 despite liver transplant. Two survived after liver transplant (Chikami et al., 1993).

It was postulated that FIAU may have caused irreversible damage to cellular mitochondrial DNA, resulting in widespread, severe multiorgan failure (Chikami et al., 1993). Such damage may be cumulative and progressive, accounting for the delayed toxicity (Chen et al., 1991). The FIAU trial tragedy has raised the possibility that other nucleoside analogs may also give rise to delayed toxicity, especially after prolonged usage. These findings are likely to influence the design of future trials of nucleoside analogs (Macilwain, 1993).

There has been considerable interest in the dideoxynucleosides in the treatment of CHB. These agents inhibit polymerases and have a high affinity for reverse transcriptase. They have demonstrated inhibition of replication of duck HBV (Kassianides et al., 1989). AZT (zidovudine, 3′-azido-3′deoxythymidine) treatment however, had no appreciable effects on HBV DNA in HIV patients with CHB, despite long term therapy (Gilson et al., 1992; Marcellin et al., 1989b). AZT is metabolized in the liver so effective levels of the active triphosphate may not be present in hepatocytes. The drug has not been studied in immunocompetent patients. Results may be more promising in patients with HIV and CHC. Biochemical and histological evidence of CHC remission was seen after 9 months of AZT treatment in 8 of 9 patients (Vento et al., 1991), but HCV RNA was not measured. Whether AZT directly affects HCV replication or merely improves T-helper cell function (or both) to give the favorable response is not clear. Immunocompetent CHC patients have not been treated with AZT.

Six patients with both HIV and CHB were treated with ddI (2′, 3′-dideoxyinosine) to assess the effect of this dideoxynucleoside on HBV replication. Only 1 of the 6 demonstrated HBV DNA suppression (Catterall et al., 1992). Seven immunocompetent CHB patients were treated in a dose escalating study with ddI. No appreciable effect on viral replication was noted (Fried et al., 1992C). The lack of effect on patients with CHB was felt to be due possibly to decreased phosphorylation in hepatic cells when compared to lymphoid cells. Alternatively, high levels of naturally occurring nucleosides in hepatocytes may compete with the incorporation of ddI into the growing viral DNA, thus hindering chain termination. Higher doses could be considered but toxicities are significant and dose-related (Fried et al., 1992C). It is of interest, however, that ddI appears to be the least toxic to mitochondrial DNA in in vitro studies using a human lymphoblastoid cell line (Chen et al., 1991).

Another dideoxynucleoside, 3TC (3′-thiacytidine, lamivudine) is a more recently developed compound which appears to be more promising than ddI as a potential treatment for CHB. It is well tolerated in patients with HIV. In vitro studies have shown inhibition of both human and duck HBV replication. Oral administration of 3TC in a phase I/II study to patients with CHB for 1 month showed that all tested doses inhibit HBV replication as evidenced by reduced serum HBV DNA. After treatment was completed, however, rebound HBV DNA was observed. There were no serious adverse events associated with the drug in a 2 month follow-up observation period (Tyrrell et al., 1993). A phase III multi center study is currently in progress assessing the efficacy of 3TC in CHB.

While nucleoside analogs appear to hold some promise in the treatment of CHB, and in some instances CHC, suppression of viral replication seems to be more common than clinical cure. Long term studies will have to be performed with extreme caution as it appears that large cumulative doses may give rise to serious or fatal consequences, due to mitochondrial DNA or other toxicities (Chen et al., 1991). Combinations of antiviral agents or immunomodulatory and antiviral agents may offer more promise at this time by reducing severe toxicities. Alternatively, novel cellular targeting systems could be safer and more effective (Ponzetto et al., 1991). Chronic suppressive therapy with single agents or a combination of agents might be useful if non-toxic effective doses can be achieved.

1.7. Bile acid therapy

In the past 10 years there has been interest in treating chronic liver disease, particularly cholestasic illnesses, with bile acids. Different bile acids have different effects on liver cells, depending on the degree of hydroxylation of the bile acid and the orientation of the hydroxy groups, resulting in more or less hydrophobicity. The more hydrophobic the bile acid, the more lithogenic it becomes. Cholestasis and hepatocellular damage with associated hypertransaminasemia has been observed in clinical trials of gallstone dissolution with chenodeoxycholic acid. On the other hand, striking improvements in liver enzymes were observed in patients with primary biliary cirrhosis treated with the hydrophobic bile acid ursodeoxycholic acid (UDCA) in an uncontrolled study (Poupon et al., 1987). The proposed mechanism, for clinical benefit in chronic liver disease, is that treatment with UDCA make bile less toxic for hepatocytes by reducing the fraction of the toxic hydrophobic bile acids (Podda et al., 1988).

Consistent decreases in serum transaminase levels were found in 6 patients with chronic active non-A, non-B hepatitis during treatment with UDCA for gallstone dissolution (Leuschner et al., 1985). Five of the 6 patients had liver biopsies prior to starting therapy. Two of the five patients underwent repeat biopsies, after therapy showing a decrease in inflammatory activity and a disappearance of piecemeal necrosis. Based on these studies several more investigations were performed to examine the effects of UDCA in chronic hepatitis.

UDCA treatment of patients with chronic hepatitis resulted in significant improvement in serum transaminase levels compared with placebo or taurine administration to generate taurine-conjugated bile acids which are more hydrophilic than

glycine conjugates (Glezzi et al., 1987; Podda et al., 1990). The effects of UDCA did not appear to be dose-dependant. Osuga et al. (1989) also studied UDCA in patients with chronic hepatitis. They showed significant improvement in liver chemistries but did not report the final histological evaluations in their paper.

UDCA appears to be a safe and potentially effective drug in the treatment of chronic hepatitis perhaps as an adjunct to other therapies. The majority of the patients thus far evaluated have chronic non-A, non-B/CHC hepatitis.

2. Future directions

There are a variety of immunomodulatory and antiviral agents which have been shown to decrease viral replication in CHB and CHC. These antiviral effects have been variable and associated with a spectrum of toxicities. It is most likely that a combination of agents, particularly one incorporating an antiviral with an immune-modulatory, will result in the most effective approach to the treatment of chronic viral hepatitis.

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