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ORIGINAL ARTICLE

Ribavirin/interferon-α sequential treatment of recurrent hepatitis C after liver transplantation

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Abstract Hepatitis C virus (HCV) infection invariably recurs after liver transplantation (LT), and sequels of chronic hepatitis of the graft are a significant cause of morbidity and mortality. In an uncontrolled trial, 31 patients with histologically confirmed hepatitis C after LT received, sequentially, ribavirin (10 mg/kg body weight q.d.) for 12 weeks, followed by ribavirin at the same dose q.d. plus interferon-α (IFN-α) [3 million units three times a week (3 MU TIW)] for another 48 weeks. Based on an intent-to-treat analysis, the percentages of patients with undetectable HCV RNA in their serum were 0%, 38.7% and 45.2% after 12, 36 and 60 weeks of therapy, respectively. A sustained virological response, as defined by undetectable serum HCV RNA 24 weeks after the end of treatment, was observed in 9/31 patients (29%). Sustained responders had a significant improvement of their liver inflammatory activity score ($P = 0.025$), but not of their liver fibrosis score. The chances of sustained virological response correlated with the length of treatment, but not with the HCV genotype or baseline HCV RNA level. In conclusion, patients with recurrent hepatitis C after LT might benefit from ribavirin/IFN-α therapy, provided that the treatment is tolerated for a sufficient duration of time.

Keywords Hepatitis C virus · Graft rejection · Chronic hepatitis · Liver cirrhosis

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Introduction

Cirrhosis caused by the hepatitis C virus (HCV) is the leading indication for liver transplantation (LT) among adults, both in the USA and in Europe. One out of four LTs currently performed in the USA is for HCV-related cirrhosis [1].

The recurrence of HCV infection occurs early after LT and is almost universal. Histologically confirmed recurrent hepatitis C in the grafted liver may occur in up to 70% of patients during the first year after LT, and approximately 20% may rapidly progress to graft failure or cirrhosis, leading to death or re-transplantation. The morbidity associated with recurrent HCV infection has not been shown, so far, to affect the overall mortality rate, at least during the first 5 years after LT [2]. Nonetheless, the progression of recurrent hepatitis C after LT towards cirrhosis [3] and liver failure [4] seems accelerated when compared with immunocompetent individuals.

A standard treatment for recurrent hepatitis C after LT has not been established. Both interferon-α (IFN-α) and ribavirin have been used in this clinical setting, both as monotherapy and as a combination of the two, and either as prophylaxis or as therapy for histologically confirmed recurrent hepatitis [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]. In most studies, the rate of response, either biochemical or virological, was low. Moreover, an untoward immunostimulation, resulting in allograft rejection, has been occasionally described in some early reports [9, 10, 11, 14, 15, 19, 20, 22]. To avoid induction of rejection, some authors have suggested that IFN-α be given later in the post-LT period, or with increased immunosuppression, or associated with ribavirin. More recent studies, in fact, suggest that a combined regimen using IFN-α and ribavirin does not seem to increase the risk of graft rejection [6, 7, 13, 16].

Ribavirin is a guanosine analogue, effective against several RNA and DNA viruses. Although its administration as a monotherapy to patients with recurrent hepatitis C after LT is mostly followed by a decrease in ALT level, this does not seem to be accompanied by an antiviral effect, since serum HCV RNA levels remain unaffected [12]. Ribavirin may cause haemolytic anaemia, which is sometimes so severe as to require dose reduction [7, 17, 18], but this effect can be corrected by the administration of erythropoietin [6, 17]. Ribavirin not only does not increase the risk of rejection but, in the experimental model of skin allograft, also seems to potentiate the immunosuppressive effect of cyclosporine [25].

The results of the clinical trials using a standard IFN-α/ribavirin combined regimen show that the overall efficacy is lower than that obtained in immunocompetent, chronic hepatitis C patients, with a sustained virological response ranging between 10% and 33%, with frequent, prominent side effects being reported in most studies [5, 6, 8, 13, 14, 26]. An optimal schedule, however, has still to be identified.

In the present clinical trial, we treated 31 consecutive patients presenting with recurrent hepatitis C after LT with a sequential administration of ribavirin (for 12 weeks) followed by the ribavirin/IFN-α combination for another 48 weeks. The rationale behind this schedule was the exploration of the possibility of treating patients early after LT with a ribavirin monotherapy, while delaying the IFN-α administration by 12 weeks, in order to reduce the risk of graft rejection. In addition, we took the opportunity to study the intrahepatic expression of Th1/Th2 cytokines before and during ribavirin monotherapy. The conclusions of the latter analysis have been published recently [27], and we present now the final results of the clinical trial.

Patients and methods

Patients

A total of 31 patients was included in an open-label, uncontrolled, clinical trial. Their baseline features are summarized in Table 1. There were 23 men and eight women. The median age at inclusion was 54 years (range 39–65 years). The HCV genotype was 1 in 19 cases (61%), 2 in four (13%), 3 in four (13%), and 4 in three patients (10%). One patient had a mixed infection (types 2 and 4).

Inclusion criteria were: age between 18 and 65 years, having undergone a LT for end-stage liver disease due to HCV, presence of HCV RNA in serum by a qualitative reverse transcriptase–polymerase chain reaction (RT-PCR) assay (see below) and recurrent hepatitis of the graft, diagnosed at histology no less than 3 months after LT and within the 3 months prior to inclusion in the trial. Exclusion criteria were: liver re-transplantation for

Table 1 Baseline features and virological outcome of 31 patients with recurrent hepatitis C after LT who were studied in the present clinical trial (*CyA* cyclosporine A, *MMF* mycophenolate mofetil, *RR* responder–relapser, *NR* non-responder, *SR* sustained responder, *DO* drop-out, *NA* not available)

No.	Gender	Age (years)	HCV type	Immunosuppression at baseline	Time from LT (months)	Serum HCV RNA				Virological outcome
						Baseline	Week 12	Week 36	Week 60	
1	M	47	3	CyA	5	17,500,000	6,630,000	–	–	RR
2	F	45	1	CyA	22	1,850,000	241,000	–	+	NR
3	F	58	1	CyA, azathioprine	23	NA	NA	NA	NA	DO week 3 (NR)
4	M	49	3	Tacrolimus	9	626,000	5,040,000	–	–	RR
5	M	52	1	Tacrolimus, prednisone	16	2,220,000	2,115,000	–	–	SR
6	M	53	1	CyA, azathioprine, prednisone	3	NA	NA	+	–	DO week 48 (NR)
7	M	45	4	CyA, azathioprine	84	1,124,000	Na	+	–	RR
8	M	55	1	CyA, azathioprine	93	NA	NA	NA	NA	DO week 2 (NR)
9	M	60	1	Tacrolimus	5	NA	NA	NA	NA	DO week 10 (NR)
10	M	54	3	Tacrolimus	16	226,000	468,000	–	–	SR
11	M	39	3	Tacrolimus, prednisone	6	3,000,000	2,160,000	–	–	SR
12	M	59	1	CyA	10	2,460,000	1,300,000	–	–	SR
13	M	55	1	CyA	73	113,000	55,700	–	–	SR
14	M	64	2	CyA, azathioprine	28	NA	NA	NA	NA	DO week 20 (NR)
15	M	56	2	Tacrolimus, prednisone	3	56,500,000	7,050,000	+	+	NR
16	M	51	4	Tacrolimus	85	472,000	NA	–	–	RR
17	F	58	2	Tacrolimus	12	2,360,000	1,896,000	–	(–)[a]	DO week 48 (SR)
18	M	53	1	CyA	7	1,380,000	NA	+	+	NR
19	M	40	1	CyA	3	NA	NA	NA	NA	DO week 3 (NR)
20	M	53	1	CyA, MMF	9	4,180,000	NA	+	+	NR
21	F	57	1	Tacrolimus	39	1,250,000	830,000	+	+	NR
22	M	52	1	Tacrolimus	33	1,498,000	1,580,000	+	+	NR
23	F	64	2/4	CyA	84	147,200	90,000	–	–	SR
24	M	59	1	CyA	8	NA	NA	NA	NA	DO week 8 (NR)
25	F	55	2	CyA	18	1,030,000	810,000	+	+	NR
26	M	65	4	Tacrolimus	24	1,134,000	1,560,000	+	+	NR
27	M	49	1	Tacrolimus	24	871,000	NA	+	+	NR
28	M	52	1	CyA	59	770,000	NA	NA	–	SR
29	M	64	1	Tacrolimus	8	2260000	NA	+	+	NR
30	F	61	1	CyA	49	53,400,000	4,960,000	–	–	SR
31	F	52	1	Tacrolimus	3	NA	NA	NA	NA	DO week 11 (NR)

[a]As determined at week 48, when the patient's therapy was abandoned (see text)

rejection or for recurrent hepatitis C on the graft, history of severe cardiovascular disease, presence of HBsAg and/or HIV, history of auto-immune disease (including auto-immune hepatitis), alcohol consumption >40 g/day, acute rejection within the 6 months prior to inclusion, unresolved biliary complication, renal insufficiency (serum creatinine levels above 200 μmol/l), neutrophil count less than 1,500/mm^3, platelet count less than 75,000/mm^3, haemoglobin below the lower limit of normal, alpha-fetoprotein above the upper limit of normal, hepatic arterial thrombosis, pregnancy or breast-feeding, psychosis or anti-depressant therapy for uncontrolled clinical depression, clinically significant retinal abnormalities, thyroid dysfunction, and history of chronic haemolytic anaemia.

The study was approved by all ethical committees of the participating centres and performed in accordance with the standards of the Declaration of Helsinki. All patients gave their informed consent prior to their inclusion in the study.

Treatment schedule

All patients were allotted to the same treatment schedule. The therapy consisted of a first period of ribavirin monotherapy at a dose of 10 mg/kg/day for 12 weeks, followed by ribavirin at the same dose combined with interferon-α_{2b} (Intron A, Essex Chemie AG, Luzern, Switzerland) at a dose of 3 MU TIW for another 48 weeks. The main rationale for this unusual schedule lay in the fact that our delaying the start of Intron A treatment would limit the risk of inducing graft rejection. At the same time, ribavirin, which is not known for posing the risk of graft rejection, was to be administered as soon as the histological diagnosis of recurrent hepatitis was made. In addition, total RNA extracted from liver biopsy samples taken before and during ribavirin monotherapy allowed us to analyse the changes in Th1/Th2 cytokine levels induced by this drug [27]. After the end of therapy (even if prematurely withdrawn), patients were still followed-up for another 24 weeks.

Serum assays

Serum HCV RNA was evaluated by a qualitative RT-PCR (COBAS Amplicor HCV, Hoffman–La Roche, Basel, Switzerland; sensitivity limit 50 UI/ml) at entry, at the end of therapy, and the end of the follow-up. A quantitative assay (COBAS Amplicor HCV Monitor, Hoffman–La Roche; sensitivity limit 500 UI/ml) was performed in selected patients at the start of ribavirin therapy as well as at the start of the combination. HCV genotypes were evaluated by a commercially available line-probe assay (INNO-LiPA, Innogenetics, Antwerp, Belgium).

Histological assessment

A liver biopsy was obtained from all patients before inclusion, so that we could assess the presence of recurrent hepatitis and rule out histological signs of graft rejection. Further liver biopsies were performed only when clinically indicated or once a year (in patients followed-up at selected locations, according to local follow-up protocols). Histological diagnoses were established in accordance with internationally accepted criteria [28, 29, 30]. Sections were stained with haematoxylin and eosin and evaluated according to a scoring system that includes the semi-quantitative assessment of liver disease grading and staging [28].

Immunosuppressive regimen

At the time ribavirin treatment was started, 17 patients were receiving, as immunosuppressive treatment, cyclosporine A (Sandimmun Neoral, Novartis Pharma, Bern, Switzerland), at a dose of 5–10 mg/kg per day, whereas 14 patients were given tacrolimus (Prograf, Fujisawa, Kerry, Ireland) at a dose of 0.1–0.15 mg/kg per day. Trough levels were 100–300 ng/ml for cyclosporine A and 8–15 ng/ml for tacrolimus. Additional drugs included azathioprine (Imurek, Wellcome, Bern, Switzerland) (75 mg q.d., five patients), low-dose prednisone (four patients) (which was completely withdrawn within the first 6 months of antiviral therapy) or mycophenolate mofetil (Cell-Cept, Roche Pharma Schweiz, Basel, Switzerland) (one patient). During therapy, the doses of cyclosporine A and tacrolimus were occasionally adjusted, according to blood levels.

Statistical calculations

Differences among groups were evaluated by the Fisher test. Viraemia variations over time in the same patients were evaluated by the Wilcoxon rank sum test.

Results

Overall tolerability

Ribavirin monotherapy, which was started a median of 18 months from LT (range 3–93 months), was rather poorly tolerated, with symptoms related to anaemia being the most relevant side effect. Six patients had their treatment interrupted during the first 12 weeks. Severe anaemia (<8 g haemoglobin/dl) was the cause for withdrawal in four, whereas progressive worsening of liver function due to cholestatic fibrosis was the reason for permanent therapy discontinuation in the remaining two. Both latter patients died within 2 weeks of being dropped from the study, but their deaths were deemed to be unrelated to ribavirin. As a result of these early withdrawals, only 25 patients went ahead to receive also IFN-α as per schedule, i.e. at the end of the 12-week ribavirin monotherapy. After starting the combination, three more patients had to discontinue the therapy prematurely: one was stopped after 2 months of combination, due to severe anaemia (<8 g haemoglobin/dl), and the other two patients were withdrawn from the study after 11 months of combined regimen, due to severe weight loss ($>20\%$ of the baseline body weight) in one case, and to histologically confirmed chronic rejection in the other case (patient 6, Table 1).

Ribavirin dose reductions, not leading to discontinuation of treatment, were necessary in 11 patients: the main reason was anaemia in nine cases, intolerable pruritus in one and dyspnoea in one. Conversely, the IFN-α dose had to be reduced in two additional patients due to severe neutropenia (<0.5 g/l) or (albeit only temporarily) severe back pain. Mild neutropenia (0.75–1.0 g/l), not requiring an IFN-α dose reduction, was observed in an additional six patients. Similarly, mild thrombocytopenia (50–70 g/l) was seen in only one patient and did not require IFN-α dose adjustments.

No patient developed histological signs of acute rejection during the treatment or the 6 months of follow-up after the therapy was stopped. One patient developed chronic rejection after 11 months of treatment: he had started therapy 3 months after LT, and at the time ribavirin was introduced the liver histology had ruled out the presence of graft rejection.

Virological response

Serum HCV RNA decreased (but remained detectable in all) during ribavirin monotherapy in 12 out of 16 patients for whom these data were available. This decrease was statistically significant ($P<0.06$, Wilcoxon rank sum test). Based on an intent-to-treat analysis, serum HCV was undetectable in six (19.4%) and in 12 (38.7%) patients after 12 and 24 weeks, respectively, of combi-

nation therapy (Table 1). At the end of therapy, HCV RNA was undetectable in 13 out of the 23 patients (56.5%) who had completed the treatment as per schedule, and in an additional patient who had been withdrawn from therapy after 36 weeks of combination (patient 17, Table 1). Thus, on an intent-to-treat basis, a virological response at the end of therapy was observed in 14 patients (45.2%).

At the end of the 24-week period that followed the end of treatment, eight patients still had undetectable HCV RNA in their sera. Furthermore, another patient, who had to be prematurely withdrawn from the study after 11 months of combination regimen, due to severe weight loss, was also HCV RNA negative in her serum at the end of post-treatment follow-up (patient 17, Table 1), while the other eight patients who had been dropped from the study had detectable HCV RNA in their sera at the time they their treatment had been abandoned (data not shown). Thus, based on an intention-to-treat analysis, nine patients out the 31 who were enrolled in the trial (29%) were considered to be sustained virological responders.

Factors associated with a sustained virological response

The probability of patients' reaching a sustained virological response was not related to the serum HCV RNA level before ribavirin monotherapy or at the time the combination therapy was started, or to the fact of their having received 80% of the cumulative IFN-α or ribavirin dose, or the type of immunosuppressive therapy (Table 1). The HCV genotype did not seem to affect the response rate, although the end-of-therapy response was observed in 6/19 (31.5%) patients with type 1 and 5/8 (62.5%, i.e. twice as many) patients infected with types 2 or 3, whereas the sustained response was achieved, respectively, in 5/19 (26.3%) and 3/8 (37.5%). These differences indicated a trend but failed to reach statistical significance, due to the small sample size.

One factor associated with the sustained response was a virological response during therapy, since serum HCV RNA was negative, after 12 weeks of combination, in 5/6 sustained responders but only in 1/13 non-responders or responders/relapsers for whom serum samples were available ($P=0.0002$, Fisher's test). Similarly, serum HCV RNA was undetectable in all eight sustained responders after 24 weeks of combination, whereas none of those who still had HCV RNA in the serum at this time point progressed to a durable response (Table 2). In addition, the treatment duration appeared to affect the chances of a durable response, since 9/23 (39.1%) patients who were treated for at least 80% of the scheduled duration of therapy (>48 weeks out of a total of 60 weeks) became sustained virological responders, compared to 0/8 patients who were prematurely withdrawn from therapy ($P=0.027$) (Table 2).

Histological response

No liver biopsies were scheduled as per protocol, except for the one needed for diagnostic purposes at patients' enrolment. However, in five sustained responders and in nine responders–relapsers/non-responders, paired liver biopsies were available at baseline and 12 ± 8.51 and 9 ± 6.1 months, respectively, after the end of follow-up ($P=$NS). In sustained responders, the fibrosis score remained unchanged, whereas a significant improvement was noted in the activity score ($P=0.025$, Wilcoxon rank sum test). Among responders–relapsers/non-responders, the fibrosis score became significantly worse ($P=0.012$ by the Wilcoxon rank sum test), whereas no modifications were noted for the activity score ($P=$NS) (Fig. 1).

Table 2 Factors associated with a sustained response after combined treatment of recurrent hepatitis C after LT

Factor	SR rate (%)	P^a
Serum HCV RNA + at 12 weeks of combination	1/13	0.0002
Serum HCV RNA − at 12 weeks of combination	5/6	
Serum HCV RNA + at 24 weeks of combination	0/11	0.016
Serum HCV RNA − at 24 weeks of combination	8/12	
>80% Duration of the scheduled treatment	9/23 (39.1)	0.027
<80% Duration of the scheduled treatment	0/8 (0)	
>80% Scheduled IFN-αdose	8/22 (36.4)	0.14
<80% Scheduled IFN-αdose	1/9 (11.1)	
>80% Scheduled ribavirin dose	7/20 (35)	NS
<80% Scheduled ribavirin dose	2/11 (18.2)	
>80% IFN-α + duration	8/22 (36.4)	0.14
<80% IFN-α + duration	1/9 (11.1)	
>80% Ribavirin + duration	7/20 (35)	NS
<80% Ribavirin + duration	2/11 (18.2)	
>80% IFN-α + ribavirin + duration	6/19 (31.6)	NS
<80% IFN-α + ribavirin + duration	3/12 (25)	

[a]Fisher's test

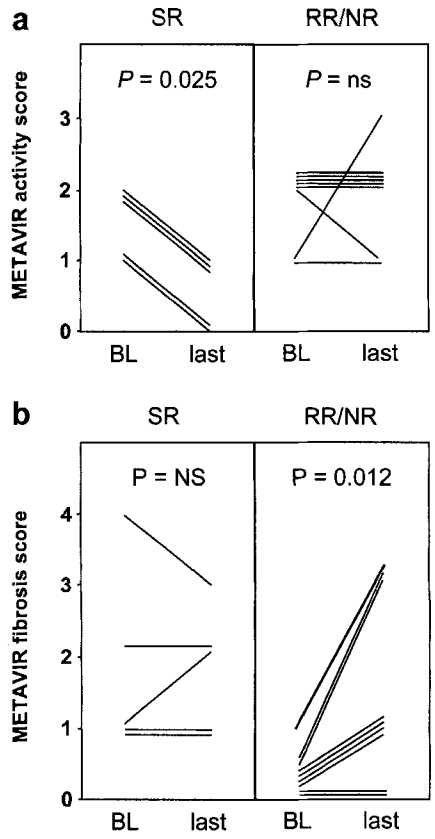

Fig. 1a, b Changes over time of the METAVIR activity score (**a**) and fibrosis score (**b**) in five sustained responders (*SR*) and nine responders–relapsers/non-responders (*RR/NR*) for whom liver biopsies were available at baseline (*BL*) and during the follow-up after the end of treatment (*last*)

Discussion

An optimal treatment schedule for recurrent hepatitis C after LT is urgently needed, in view of the risk of a rapid clinical and histological progression of this disease [2, 3, 4]. A standard combination of IFN-α and ribavirin has been widely used, and the newly available pegylated interferons have been preliminarily shown to add to the effectiveness of this approach [22, 31, 32]. The chances of a sustained response, however, must be weighed against the treatment-associated morbidity, which includes the risk of graft rejection (and possibly loss) and the anaemia associated with ribavirin, particularly severe in this setting.

Different approaches to the management of hepatitis C that recurs after LT have been proposed: low-dose ribavirin [5], starting of treatment later on after LT, or even prophylaxis of the hepatitis early after LT [16, 19, 20, 32]. Overall, the sustained response rate may vary from 5% [17] to 33.3% [16], with an average rate of approximately 20%, i.e. reduced by half when compared with the rate obtained in immunocompetent patients treated with a similar regimen [33, 34]. The risk of rejection has been particularly worrisome, since the early report of an acute vanishing bile duct syndrome following IFN-α monotherapy [9]. A statistically increased risk was reported only by one study, again using IFN-α monotherapy [10], but not by others, especially in the important, controlled study from Pittsburgh [15]. This risk, whatever its magnitude, seems to have been reduced to nil by the addition of ribavirin [6, 8, 13]. Ribavirin was shown to possess an immunomodulatory activity, which, in the rabbit model of skin allograft, may translate to an immunosuppressive effect, potentiating the activity of cyclosporine A [25]. It is not surprising, therefore, that the combined administration of IFN-α and ribavirin to LT patients may be largely favoured over IFN-α monotherapy, and not only in view of its increased efficacy. In the present study, there were no acute rejection episodes, although one patient developed chronic rejection. This patient had increased levels of total bilirubin at entry, and, although liver histology had ruled out signs that suggested an impending graft rejection, the patient was enrolled into the study. He failed to respond virologically and, after 8 months of combination therapy, was withdrawn from the study. Whether or not this patient's outcome was influenced by the antiviral therapy, is unknown.

We could not identify specific factors that predicted a sustained response, such as baseline serum HCV load or genotype, as shown among immunocompetent patients [33, 34], except for (1) virological response during therapy (i.e. after 12 and 24 weeks of combination) and (2) duration of therapy (at least 80% of the scheduled duration, i.e. >48 out of a total of 60 weeks). The first point is in agreement with other evidence reported for immunocompetent chronic hepatitis C patients [35, 36, 37]: the lack of an early virological response is unlikely to translate into a durable response later on during therapy, and, therefore, patients with HCV RNA still detectable in serum after a short test period of therapy should be withdrawn from antiviral treatment. The relevance of the duration of therapy raises the issue of its tolerability, which was rather poor in the present study, haemolytic anaemia's being the most serious cause of withdrawal encountered, as well underscored by other recent studies [17, 18]. Since most cases of intolerable anaemia occurred within the first 3 months of ribavirin monotherapy, a possible approach to the management of this serious adverse event may be an initial test period aimed at finding the highest tolerated dose of ribavirin before the IFN-α is added.

The sustained response to therapy was associated with an amelioration of the histological grading score, whereas the fibrosis score remained unmodified. Conversely, in the absence of a durable response, the fibrosis worsened, and the necro-inflammatory activity did not decrease. The increase in fibrosis score whilst on ther-

apy, in the latter group, occurred mostly during ribavirin monotherapy [27], and this is even more noteworthy if we consider the short period of time over which it was recorded. This phenomenon, which has also been reported by other investigators [7, 12], was not reversed by the subsequent combination therapy and warrants further study.

With the regimen used in the present study, a durable response was achieved in one-third of our patients, this rate rising to approximately 40% among patients who tolerated their treatment for a sufficient period of time. The use of a more effective and tolerable therapy for recurrent hepatitis C after LT is clearly warranted. Recent reports suggest a trend for an early antiviral response of pegylated IFN-α similar to that of non-LT patients [22, 31, 32]. The role of this new molecule in the management of post-LT recurrent hepatitis C, however, remains to be further assessed, especially as far as its tolerability is concerned.

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