The Misuse of Interferon Minimizes its Effectiveness in Therapy Eliciting Desensitization And Tachyphylaxis: A Different Administration Schedule May Avoid Relapse of Chronic Hepatitis C

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Abstract

Interferon (IFN) alpha is the only drug active in the therapy of chronic B and C hepatitis (CHB and CHC) and is active in several types of cancer especially Hairy Cell Leukaemia, Chronic Myeloid Leukaemia and melanoma. The present therapeutic schedules use an almost continuous administration of IFN in spite of the fact that the first IFN administration determine a striking decrease of IFN receptors and consequently tachyphilaxis and desensitization. The continuous administration does not permit the receptors recovery strongly decreasing the IFN effectiveness. It determines also the synthesis of an interleukin-1(IL-1) antagonist decreasing the antiviral effect of IL-1 and the interleukin 2 (IL-2) synthesis. Furthermore hampers the synthesis of the lambda interferons that have a strong antiviral activity whose synthesis is stimulated by the interferon alpha. Intermittent IFN administration with intervals permitting the receptors recovery should strikingly improve the effectiveness of IFN therapy decreasing at the same time its toxicity. Two cases are reported in which intermittent administration permitted the complete recovery of relapsed CHC which is almost incurable.

Main Text

Interferons (IFN) are a class of cytokines produced by almost all the cell types with antiviral and immunomodulatory effects widely used in the treatment of several important and different diseases. IFN alpha alone or in combination with ribavirin is the only drug which is effective in the treatment of hepatitis C and B, viral diseases which at present in the Western countries are the most lethal infectious disease. Unfortunately its effectiveness is limited by the fact that a small part of the patients do not react to the therapy (non responders) and a large part of the other have a relapse immediately after the end of the therapy which cannot last more than six – twelve months because of the severe side effects. IFN alpha monotherapy suppresses serum HCV viral RNA to undetectable level in 25% to 40% of chronic viral hepatitis C (CHC) patients but the initial response is transient and sustained response is documented in only about 8-9% of the patients even if may reach 20% with high doses and prolonged treatment. With the best presently used schedule of the combined treatment IFN – ribavirin about fifty per cent of the patients have a relapse (for a review see 1). In these cases a second treatment does not generally gives a better result and the patient inevitably progress toward cirrhosis, liver failure or liver carcinoma (2). In the United States approximately four million people has hepatitis C and twenty per cent progress toward cirrhosis. IFNs and especially IFN alpha give positive results also in the treatment of non viral diseases. Positive results were obtained in several types of cancer, especially in the treatment of Hairy Cell Leukaemia, Chronic Myeloid Leukaemia, Melanoma, and Kaposi Sarcoma. In Hairy Cell Leukaemia and Chronic Myeloid Leukaemia during the treatment frequently a complete or partial remission occurs but unfortunately almost all the patients relapse after the end of the treatment. IFN therapy also increases the life expectancy in patients with metastatic melanoma and Kaposi Sarcoma (for reviews see 3,4). In the treatment of all these diseases IFN is generally used nearly the maximum tolerated dose: daily or three times a week for a minimum of six months to a maximum of two–three years. Longer treatments are impossible due to the harmful side effects of the IFN therapy. With the introduction of the long life pegylated IFN the drug is administered once a week but the cells during the treatment period are permanently in the presence of the drug. In conclusion with the present schedules IFN therapy is surely of help in the treatment of some viral diseases and some types of cancer but its utility is limited by the frequent occurrence of relapses which are practically the rule in the Leukaemia treatment. The hypothesis The hypothesis is here forwarded that a large part of the relapses, at least in the cases of the CHC, are due to a misuse of the IFN which minimizes its efficacy. IFN administration has initially a very strong antiviral
activity which decreases strikingly after a single day (a common phenomenon using many drugs acting through receptors called tachyphylaxis). IFN may be used at lower doses diminishing its harmful side effects and at the same time strongly increasing its usefulness by simply increasing the intervals between the administrations. The poor results obtained insofar with the presently used schedules are due to the fact that the initial administrations of IFN drastically reduce the number of the IFN receptors on cell surfaces reducing its effectiveness; the frequent administration of the drug does not permit the recovery of receptors and consequently the schedule minimizes its effects. Furthermore the continuous administration reduces the activity of interleukin 1 (IL-1) triggering the synthesis of a IL-1 receptor antagonist and probably the synthesis of interleukin 2 (IL-2) thus decreasing their antiviral activity. Synthesis of interferons lambdas that have a strong antiviral activity (for a review see 5) should also be hampered because their synthesis is promoted by interferon alpha (5). Longer intervals would permit the receptors recovery so that the efficacy of the first administration would be maintained during the treatment. A similar treatment could possibly avoid the relapse in some types of cancer efficiently treated with interferon. Evaluation of the hypothesis Dynamic of the viral clearance In the clinical practice all the chronic B or C hepatitis are treated with alpha IFN following one of these schedules: 1) Daily administration for six- twelve months with three – ten millions units; 2) three weekly administrations with the same doses; 3) one weekly administration of 180 mg. of the long life pegylated IFN. In this case also a single weekly administration permits a constant presence of the IFN. In several researches (6,7,8,9) the clearance of HCV RNA was evaluated before and during the treatment and in all cases the responders patients the kinetics of the clearance was biphasic: a very rapid decrease clearing 25-80 % (depending on the dose) of the viral RNA occurred within one – two days. In a second time the slope of the clearing curve is much slower so that several weeks are necessary to have undetectable levels of HCV RNA. While the initial decrease is dose dependent increasing from the three million units to the ten millions units the second phase it is not dose dependent. According Neumann et al (9) the first steep slope at day 1 is related to direct IFN inhibition of virus production, whereas the second slope starting at day two appears to be related to infected cell death. Even if this hypothesis is true the biphasic shape of the curve indicates that after 1–2 days the IFN looses most of its efficacy in clearing the virions. At the end of the therapy about 80-90% of the patients treated with IFN alone and 50% treated with the combined therapy IFN–ribavirin experience a rapid relapse and the virus reaches the same or even higher level of that at the beginning of the therapy. A second treatment with the same schedule only exceptionally gives a better result (2). Interferon treatment and receptors number IFN activity is mediated by the linkage with its receptor and the contact of the cells in vitro or in vivo with the drug strikingly and rapidly down regulates the receptor number in few hours (10,11,12). Very low doses of interferon are sufficient to reduce the number of receptors which in vivo remains low till the end of the treatment. The receptor decrease varies between half and ten times in the different experiments. After 72 hours without IFN there is a complete recovery of the receptor number (11). In conclusion, considering also that the half life of the non pegylated IFN may be 10 hours and detectable amounts are present 24 hours after the administration with the standard treatment the cells never recover the original receptor number. These observations completely explain why the clearance curve of the virus is biphasic; IFN after the first day looses its efficacy because of the reduction of its receptors. This also explains why higher doses till 10 millions units increases the initial response but not the second as in the last case their receptors are completely saturated even at low doses. The importance of the receptors number is also stressed by the fact that in patients with chronic hepatitis C which are strongly responders to the interferon therapy the receptor number is significantly higher in respect to non or weakly responders (12,13,14). Interferon alpha treatment and interleukin Interferon administration initially increases the production of IL-1 (15,16) which is likely responsible of the flu like syndrome which inevitably occurs at the beginning of the interferon therapy. Very soon however interferon stimulates the production of an antagonist of IL-1 which eliminates the effect of this cytokine (17,18,19,20) and at the same time the flu like syndrome disappears. The reduction of the IL-1 activity caused by the continuous administration of interferon is particularly important because IL-1 inhibits hepatitis C RNA replication activating an extracellular kinase pathway and inducing one of the interferon stimulated genes, 1-8 U which exhibits antiviral activity (21). IL-1 does not induce another interferon stimulated gene, ISG 6-16 suggesting that IL 1 induces a novel antiviral pathways within the cell (22). Furthermore it has been shown that IL-1 inhibits HBV replication in cells that have been shown to posses an intact IL-1 receptor (2). IL-1 stimulates also the antiviral activity of IFN gamma through activation of
the nuclear factor kappa light chain (NF-kB) and consequently IL-1 antagonists strongly reduce its antiviral activity (23). In conclusion the continuous administration of interferon abolishes part of its antiviral action through the induction of circulating IL-1 receptor antagonist. The continuous administration should also reduce the production of IL-2; alpha IFN and IL-1 independently enhance IL-2 production (24,25) and therefore the reduction of the interferon receptors number and the synthesis of the antagonist to IL-1 should reduce the IL-2 synthesis. IL-2 has antiviral and antitumor properties (26,27), probably because is necessary for the T cell immunologic memory, further reducing the activity of the IFN. In summary the continuous administration of high doses of IFN alpha strikingly diminishes its therapeutic efficacy through the diminution of receptors number and the stimulation of an IL-1 antagonist at the same time increasing its harmful side effects. Interferon alpha treatment and the synthesis of interferons lambda IFNs lambda 1,2,3 also known as IL29, IL-28A and IL-28B are a newly described group of cytokines distantly related to the alpha IFN. IFN lamdas activate pathways of JAK-STAT and MAPKs to induce antiviral, antiproliferative, antitumor and immune responses. IFN alpha strongly enhance the production of IFN lambdas. The continuous treatment with IFN alpha and the decrease of the receptor number should therefore decrease the antiviral and antitumoral activity of the IFN lamda (for a review see 5). Two cases report of chronic hepatitis C treated with an intermittent schedule Twenty three years ago one of my sons was diagnosed with a non A non B chronic hepatitis further classified as C and five years later was treated with Wellferon (a mixture of various alpha IFN subtypes) for six months (one month 10 millions units three times a week, 5 months 5 millions units three times a week). However the disease relapsed less that one month after the end of the treatment. One year later his conditions were so severe that he repeated the treatment even if he was aware that a second treatment with the same dose and schedule only exceptionally produces a better result (2). After two months I completely changed the administration schedule since he was not tolerating the adverse side effects of the treatment. He maintained unaltered the dose but gradually decreased the frequency of the injections: twice a week for one month, once a week for one month, then three times in one month followed by two in one month. Then two administrations every twenty days followed by two every thirty days. The flu like syndrome started again with one administration a week but the other side effects like nausea, anorexia weight loss, fatigue, hyperthyroidism were greatly diminished. In sixteen years he did not had any relapse and the viraemia is absent. In the second case the patient is a man with liver transplant and recurrence of hepatitis C. I suggested the following treatment with recombinant interferon plus ribavirin: one month one administration a week, one month one administration every ten days, three months one administration every two weeks, two months one administration every per month. Ten months after the end of the treatment viraemia is absent. These two cases strongly suggest that an intermittent treatment may be much more effective than a continuous one. How the optimal treatment may be found When the first time changed the schedule I was ignoring all the researches quoted here; I knew only that IFN acts through receptors and that as a rule the continuous use of drugs interacting with receptors diminishes their number and consequently decreases its activity. At the same time I was also attempting to reduce the harmful effects of the treatment. It is possible of course that much better schedules may be found. Several different logical schedules may be suggested; for instance one month with standard treatment which generally in the responders gives an undetectable level of virus and then begin one administration a week; A second possibility is to immediately begin with two or one injections a week. We think that a wise system to find the optimal schedule should be to test continuously on some patients treated with different schedules the following parameters: number of interferon receptors, viraemia, alanineaminotransferase, IL-1 antagonist. Even the first three analysis are probably sufficient to reach a conclusion. These analysis, even if laborious would also permit to change the less efficient schedules during the therapy. We are confident that a schedule may be found with which all or most of the responder patients with CHC or CHB (the vast majority of cases) may have a permanent recovery. Interferon in cancer therapy IFN alpha is widely used in the therapy of various cancer types alone or in combination with chemotherapy (3,4,5). In most cases the treatment is continuous and even doses higher than those used in the antiviral therapy are used. Particularly interesting are the results that were obtained in the treatment of Melanoma and of two variety of leukaemia, the Hairy Cells Leukaemia and the Chronic Myeloid Leukaemia. IFN is the only drug which has some activity against metastatic melanoma and a few patients, about 6% may have a permanent recovery (28). In the two forms of leukaemia during the therapy a cytological complete recovery is very frequent but unfortunately most of the patients relapse at its end and with the doses used its toxicity does not permit to continue the therapy indefinitely. We think
that all the considerations we have done on its use in the antiviral therapy should be valid also in the anticancer therapy. Several researches (29,30,31,32) demonstrate that IL-1 and IL-2 are active in cancer as in antiviral therapy. We cannot know if with an intermittent administration schedule permanent recovery could be obtained but we are confident that identical or better results could be obtained drastically reducing the drug dose and its toxicity. Results of intermittent therapy could be evaluated in animal models. Conclusions Tachyphylaxis is a medical term describing a rapid decrease in the response to a drug after repeated doses over a short period of time. In the IFN case tachyphylaxis develops with the initial dose and clearly produces desensitization. Abundant evidence exists that in this case desensitization is due to a striking impairment in the receptor synthesis. This phenomenon is thoroughly considered determining the therapy with all drugs acting through receptors but not in the IFN therapies. Therapies taking in consideration this phenomenon should greatly improve its effectiveness strikingly decreasing at the same time its toxicity.

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