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Safety and efficacy of low-dose oral interferon alpha therapy in human diseases

Manfred W. Beilharz[1]* and Joseph M. Cummins[2]

[1]School of Biomedical Sciences, Faculty of Health and Medical Sciences Room, University of Western Australia

[2]Palladium Lane, Edmond, OK 73012 USA

Abstract

Publications and issued patents are discussed and summarized from studies of low dose oral interferon (IFN) alpha in humans with (a) cancers, (b) viral diseases (influenza, human immunodeficiency virus [HIV], hepatitis, fibromyalgia, papilloma viruses, measles and respiratory syncytial virus) and (c) autoimmune diseases (Sjogren's syndrome, Behcet's disease, multiple sclerosis, diabetes, multiple sclerosis and idiopathic pulmonary disease [IPF]). These studies, conducted in Africa, Asia, Australia, Europe, and North America demonstrated that IFN-α administered by the oral route is safe and effective in helping manage many diseases.

Introduction

IFNs-α are: a) cytokines exhibiting pleiotropic activity categorized as antiviral, antiproliferative and immunomodulatory, b) potent mediators in the host defense mechanism and homeostasis, modulating both the innate and adaptive immune responses, c) small (20-25kda) proteins induced in vertebrate cells by viruses, bacteria, protozoa, certain cytokines, mitogens, natural and synthetic double-stranded RNA, d) mediators of biological activities by binding to receptors present on the surface of target cells [1]. IFN-α is normally found in the body in nanogram quantities, primarily, in the nasal secretions [2]. The contents of the nasal secretions move into the oral and pharyngeal cavities. The low concentration of IFN-α in the nasal secretions serves as a guide as to how IFN-α might be used to treat disease. This paper reviews clinical data in which low-dose IFN-α was given orally, sometimes in blinded controlled studies, to patients with various diseases. Significantly, low-dose oral IFN-α is inexpensive, non-toxic, easy-to-administer, and efficacious in some cancers, infectious diseases and autoimmune diseases.

The kidney efficiently filters IFN-α from the blood. Despite this fact, pharmaceutical companies developed milligram doses of IFN-α to be injected into humans at 1000 times the endogenous concentration. Injected in milligram quantities, IFNs are toxic [3]. IFNs were not developed for oral administration because IFN given orally could not be detected in the blood of rabbits [4], dogs [5] or African Green Monkeys [6]. More than 20 years later, the expression of thousands of genes was reported to be modified by low-dose oral human IFN-α (HuIFN-α) given to cattle [7]. Gene arrays were not tested in these rabbits, dogs and African Green Monkeys given oral IFN so the development of IFN-α in human medicine proceeded with the injection route of administration whereby a blood level of IFN could be detected.

The old dogma that IFNs are species-specific is only partially correct. Examples of cross species reactivity both in vitro and in vivo are known. HuIFN-α can be orally given to cattle [7]. Recombinant feline IFN omega (IFN-ω) protects oysters against virus [8].

Cancer

The studies reviewed in this section are focused only on low-dose oral IFN-α treatments against various cancers and exclude all high-dose oral and systemic treatments where results have been poor. A study of 57 advanced disseminated anorectic (at least 5% weight loss) cancer patients was conducted to test low-dose oral IFN's effect on appetite and quality of life in wasting cancer

patients. Recombinant HuIFN-α 2a was given orally once daily for 7 days and no treatment for 7 days altering for 91 days. The daily doses tested were 0.0, 0.05, 0.5, and 5.0 IU per kg body weight. The patients given IFN doses had half as many deaths as controls in the study. Patients given the 5.0 IU HuIFN-α dose had better appetite improvement and/or weight gain than controls 5 weeks after the study began [9].

IFN-α in contact with the oral or pharyngeal mucosa reduced the side effects of radiation or chemotherapy in cancer patients [10]. Eleven head-and-neck cancer patients treated with 5 fluorouracil (5FU) for 14 days were given 150 IU natural HuIFN-α orally once daily. Six of 11 had a reduced amount of stomatitis that was expected to occur with 5-FU treatment [11].

IFN-α in contact with the oral or pharyngeal mucosa was safe and efficacious in treating malignant lymphoma and mesothelioma [12]. The IFN used orally was natural HuIFN-α given twice daily at 0.7 IU per pound of body weight. The 'terminal" lymphoma patient treated for 3 weeks went into remission and was pronounced cured in 6 months. The mesothelioma woman was 82 years old when oral bovine IFN-α therapy started; she lived 58 months.

Successful treatment of two skin melanomas with natural bovine IFN-α was reported [13, 14]. The dose of oral bovine IFN-α that was beneficial in these 2 melanoma patients and a 3rd melanoma patient [15] was 2000 units daily for 5 days followed by a week without treatment and repeated at least 4 times.

A study of oral HuIFN-α in 25 cancer patients who had failed to respond to one or more rounds of chemotherapy was reported [16]. Patients were enrolled to once daily oral dose of 1-16 IU of HuIFNα 2a per kg body weight for 8 weeks. Overall, the authors were not impressed with the clinical response but 5 patients experienced slowing of progression (3 cases of follicular lymphoma stable for 1-3 month, 1 case of renal cell carcinoma stable for 20 months and 1 case of mesothelioma stable for 3 months) after oral IFNα.These cancer patients had failed to respond to one or more rounds of chemotherapy so any positive response was unexpected. It may have been useful to continue oral HuIFNα for more than 8 weeks in these 5 cases.

Japanese scientists conducted a study of the effect of oral lowdose 200 IU of natural HuIFN-α on natural killer (NK) cell activity in human volunteers. Treatment was given daily for 4 weeks.

Compared to placebo, IFN-α treated volunteers had enhanced cytolytic activity of peripheral blood mononuclear cells on K562 and U937 cells. Two weeks after stopping IFN treatment, cytolytic activity was no longer enhanced [17]. Jim C. was diagnosed with renal cell carcinoma 6 years ago. He was given chemotherapy but the cancer spread to the lung. Jim stopped chemotherapy and took 40 units of natural bovine IFN-α orally twice daily 5 years ago. He was free of cancer when last checked in late June 2018 [18].

Fifteen children (aged 3-15 years old) with childhood neoplasia were enrolled to be given oral natural HuIFN-α (12.5-150 IU) once daily. Six patients (group A) had progressing tumors (osteosarcoma, retinoblastoma, neuroblastoma, teratoma malignum, endothelial sarcoma or rhabdomyosarcoma embryonale) and 9 children (group B) had completed successful oncological treatment (8 patients with Wilms tumor and 1 patient with lymphoma). Group A patients were treated 91-250 days (mean 188 days) and group B patients were treated 122-335 days (mean 216 days). One prominent feature of natural HuIFN-α treatment was a reduction of frequency of infections, improved appetite and enhanced feeling of well-being [19].

Twelve progressive cancer patients (10 with colorectal cancer and 1 each with lung and ovarian cancer) with liver metastasis were treated daily with low-dose oral HuIFN-α (150 IU) and Hu. In addition, the patients were injected 5 consecutive days every 4 weeks with IL-2 (100,000 IU), HuIFN-γ (150,000 IU and HuIFN-α (10,000 IU) into the liver tumor border. Regression of tumor was noted in 4 cases, stabilization occurred in 4 cases and 2 cases each progressed or died [20].

***Corresponding author:** School of Biomedical Sciences, Faculty of Health and Medical Sciences Room 1.4, L Block QEII MC , University of Western Australia, Email: manfred.beilharz@uwa.edu.au

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Viral Diseases

1. Influenza. According to estimates [21] between 291,000 and 646,000 people die each year worldwide from seasonal influenzarelated respiratory illnesses. Most of the people of the world exposed to influenza either cannot afford, or may not have access to, influenza vaccines or antiviral drugs. Oral or nasal delivery of IFNα has been reported to be safe and effective against influenza in humans. IFNα sprays or lozenges are inexpensive, non-toxic, easy-to-administer, room temperature stable, exert systemic beneficial effects and fit the medical needs of the developing nations.

Publications are reviewed herein which describe the safety and efficacy of low-dose oral IFNα given to humans during or before natural or experimental influenza virus infections. Several influenza natural outbreaks or challenge studies have been conducted in man which demonstrate that low doses (but not high doses) of intranasal or oral IFN-α may be safe and effective. When leukocyte HuIFN-α was given in low doses intranasally for 3 consecutive days to 374 subjects "at the height" of an influenza outbreak, IFN-α-treated subjects had less severe illness than 382 subjects given placebo. When IFN-α was given to 320 subjects "before" the influenza outbreak, these subjects had less illness than the 317 subjects given placebo. It was reported that the IFN-α treatment was free of adverse events and that IFN-α **provided a means for fighting virus infections [22]**. Approximately 14,000 people participated in controlled studies of placebo versus IFN-α treatment during a natural outbreak of Hong Kong influenza [23]. IFN-α (about 128 units) or placebo was dripped into the nose daily for 5 days starting about the time of the first reported influenza cases. IFN-α treatment significantly ($P<0.01$) reduced the number of influenza cases.

Efficacy of leukocyte HuIFN-α against Hong Kong influenza

Group	Treatment	Number of patients		% sick
		Enrolled	Sick	
Adults	Interferon	2994	231	7.7
	Placebo	3129	551	17.6
Children 7-12 years	Interferon	1917	119	6.2
	Placebo	2055	413	20.1
Children 2-6 years	Interferon	463	22	4.8
	Placebo	454	53	11.7

In his discussion, Soloviev stated that **"there are sufficient grounds to recommend human leukocyte-produced interferon as one of the means of influenza prophylaxis. The method is absolutely harmless, simple and convenient, and should be applied where**

there is an immediate threat of infection, that is, as a means of emergency prophylaxis."

US scientists visited the Soviet Union and reported that there was advanced clinical work on the use of exogenous IFN-α in Russia. Furthermore, the US delegation reported that leukocyte HuIFN-α was available through pharmacies in the Moscow area for use as a nasal spray against influenza [24]. Another group of US scientists arrived in Moscow during the waning days of an extensive influenza epidemic [25]. During the peak of the epidemic, the number of influenza cases reported in Moscow reached 90,000 per day. The US scientists reported that Russians were using two types of live vaccines to treat and prevent influenza. Although "one director of the institute indicated that neither live vaccine nor exogenous IFN-α was useful in the prevention of influenza," it was reported that for 3 years several Soviet medical centers observed that leukocyte HuIFN-α was effective in the prophylaxis of influenza. When treatment (500 IU leukocyte HuIFN-α was given by nasal spray three times daily for 3 days and then once daily for two days) was started in a factory or school immediately after the first case of influenza, approximately a 60% decrease in influenza symptoms was reported in HuIFN-α-treated patients, without adverse events. To achieve therapeutic effects, leukocyte HuIFN-α was given by aerosol and orally. At the first sign of influenza illness, 600 IU HuIFN-α was given over duration of 5 minutes by the oral and nasal aerosol routes. This was repeated in 2 hours if the patient's symptoms were severe and was always followed by intranasal administration of leukocyte HuIFN-α twice daily for three days at the dosage used for prophylaxis.

Clinicians reported that the IFN-α treatment caused symptoms to disappear more quickly; fever and headache were reported to clear almost immediately[25].

It was reported from Bulgaria that there was a therapeutic and prophylactic benefit of "160 units" of IFN-α given 5 times a day for 3 days (therapeutic) or 160 units given 3 times a day for 3 days repeated twice at 10-day intervals (prophylactic). No allergic or adverse events were observed in any of 868 children, including newborns and premature babies given IFN-α during a natural outbreak of influenza A (Port Chalmers variant). The author [26] reported that IFN-α therapy reduced the severity and duration of disease, especially if started on the first day of illness. Furthermore, the author reported that oral IFN-α was effective in preventing influenza. Intranasal drops of HuIFN-α (5,000 IU/daily) for 4 months reduced the frequency and severity of disease due to influenza A (H_3N_2 and H_1N_1) and parainfluenza virus [27]. Data was collected on 83 volunteers in the study. Fever occurred in only 6 of 40 volunteers given IFN-α compared to15 of 43 volunteers given placebo ($P<0.01$). Subjective symptoms of influenza such as headache, cough, fatigue, anorexia and myalgia occurred in only 34% of volunteers given HuIFN-α and in 67% of volunteers given placebo ($P<0.01$).

Leukocyte HuIFNα (10,000 IU/day) or placebo was dripped into the nostrils of 27 children daily for 60 days. The children lived in an orphanage where natural outbreaks of influenza A and influenza B occurred during the treatment period. IFN-α did not prevent illness but significantly reduced the duration of fever and the mean peak fever. Clinical manifestations of influenza were milder in children given IFN-α compared to placebo. Adverse events due to IFN-α therapy were not observed [28].

During influenza epidemics in 1983 to 1985, 140 children were treated with a spray of natural HuIFN-α into the nose and mouth twice daily for 3-4 days. The total daily dose of HuIFN-α was 700-1600 IU. The 53 control children were given traditional Chinese herbs. Children given HuIFN-α had significantly ($P<0.01$) faster normalization of temperature at 24, 36 and 48 hours after the first treatment. The clinicians reported that pharyngitis and lymphadenosis of the posterior pharynx improved when fever subsided [29].

In Japan, 73 human volunteers were randomly allotted to be administered either placebo or leukocyte HuIFN-α by nasal spray (50,000 IU divided in each nostril twice daily) for 8 weeks. However, dosage compliance was poor; only 15% of volunteers took 90% of their assigned dose in 8 weeks. Even with this compliance issue, the authors reported that the IFN-α-treated group had significantly ($P <0.05$) fewer symptoms of respiratory disease. Natural outbreaks of influenza A & B and respiratory syncytial virus occurred with influenza A the virus most commonly isolated [30].

The observations made on thousands of influenza cases given oral IFN were dismissed because it was not believable that such trivial doses of impure IFN-α could not have an effect [31]. After all, 11 volunteers given 800,000 units of IFN-α were not protected against a challenge of influenza B [25], a benefit was not noted in 13 volunteers given 35 million units of IFN-α challenged with influenza A [32], a benefit barely occurred from 70 million units of IFN-α given each of 16 volunteers before they were challenged with influenza A [33]. The Soviet observations made no sense to Western scientists when compared to studies in which high-dose IFN-α failed to provide a clinical benefit.

Did anyone in the West test IFN-α administered orally or intranasally by low dose? No, testing was not conducted using low doses because "theoretically," it could not work and it did not fit the generally accepted "more IFN is better" philosophy. When Japanese scientists tested low-dose IFN-α, benefits were reported from 5,000 IU IFN-α daily and from 10,000 IU IFN-α daily [27, 28]. However, volunteers given 50,000 IU IFN-α daily did not do as well [30] as those with lower doses [22, 23, 26]. Perhaps the Soviet and Bulgarian claims of a benefit from a few hundred units, [22, 23, 26], Chinese claims of a benefit from 700-1600 units [29], Japanese claims of a benefit from 5,000 units and 10,000 units IFN-α [27, 28] should be reexamined. Low-dose oral or intranasal IFN-α should be tested rigorously using the pure IFN-α formulations available today. Influenza is too important to dismiss all the low-dose IFN-α data.

An oral IFN/flu study was conducted in 200 volunteers in Australia during a swine flu outbreak. The volunteers were given placebo or 200 IU natural HuIFN-α from Hayashibara Biochemical Laboratories (HBL) daily during the influenza season. Post hoc analysis of participant groups identified significant reductions in the incidence of acute respiratory illness (ARI) reported by males, those aged 50 years or more and those who received seasonal influenza vaccine. The overall incidence of ARI was not limited as in previous studies, but low-dose IFN-α prophylaxis reduced the severity and duration of symptoms [34].

Human Immunodeficiency Virus (HIV). A letter to the editor of The Lancet first described the benefits of oral IFN-α in an AIDS patient [35]. Now 31 years later, oral IFN-α is rarely used in HIV+ patient despite many published reports on clinical efficacy observed with oral IFN-α, the ease of administration, lack of toxicity, room temperature

stability and low cost. Oral IFN-α may have a role in helping manage AIDS [36].

In October 1989, ACM (anhydrous crystalline maltose) powder containing natural HBL HuIFN-α was carried from Japan to Kenya to treat AIDS patients. About a week after the study started, the first 6 patients were experiencing nausea. Because of the nausea, the treatments were reduced to once a day instead of twice a day and reduced the amount of a single dose from "250 IU" to "200 IU". Frankly, exactly what dose was given was unknown because the powdered ACM-IFNα was given in tiny volumes measured with the clip off a Bic pen; this amount of powder was then rolled in aluminum foil.

Subsequently it was learned that the ACM powder would only keep the HBL HuIFN-α stable if the moisture content stayed below 2%. Exposed to the air, the ACM powder rapidly attracts moisture. Therefore, the HuIFN-α activity contained in the powder given to patients in Nairobi is unknown. After the HuIFN-α dose was reduced in mid-October 1989, remarkable clinical improvement was reported in HuIFN-α treated patients. Patients became asymptomatic and reported improved appetite and increased sexual drive. Even more impressive were the laboratory reports of greatly improved blood counts. The "CD4+ lymphocyte counts," then the most accepted measure of progression of AIDS, were reported to improve from very low counts (<200 CD4+ cells per cu. mm) back to normal (>800 CD4+ cells per cu. mm). Over the next few weeks, clinical data on 42 patients were reported [37].

Because of the impressive laboratory and clinical data, it was agreed that a blinded, placebo-controlled study was needed; HBL in Japan was asked to prepare placebo and different doses of natural HBL HuIFN-α for such a trial. By January 1990, HBL prepared thousands of individually foil-wrapped HuIFN-α lozenges containing placebo (white foil), 2 IU per lozenge (blue foil), 20 IU per lozenge (yellow foil) or 200 IU of HBL HuIFN-α per lozenge (green foil) that were delivered to Kenya.

In early January 1990, it was expected that the free lozenges would be distributed to AIDS patients so it could be learned if the earlier clinical observations were reproducible. Unfortunately, the eventual disposition of these lozenges became a mystery. Some of these placebo and active HuIFN-α lozenges became commercially available and were sold in Kenya.

In November 1989, a public announcement was made that a remarkable new AIDS treatment had been discovered named KEO89. In February 1990, the new AIDS "wonder drug" was called "KEMRON®." The Kenyan press carried bewildering, inaccurate claims. KEMRON® was "manufactured in a secret Nairobi laboratory" in one report. In another story, the KEMRON® was "manufactured" and "invented" in Kenya and the country of Kenya was going to benefit from royalties and recognition of this Kenyan invention. Suddenly there was great pride in Kenya that someone in "Black Africa" had developed a "cure" for African AIDS.

In the spring of 1990, stories reached the US that KEMRON® was selling for $40 (US) per dose in Africa. Apparently, some of the lozenges of HBL HuIFN-α delivered free for the double-blind, placebocontrolled study were being sold. The stories of KEMRON® sales and the claims in the press of an "African cure" for AIDS cast a cloud of suspicion over KEMRON® dealings in Africa. A physician in Uganda said he had purchased KEMRON® in white and blue foil. Since the white ones were placebo, he was asked how his patients were doing. He reported that the 4 patients who took the white lozenges died but that the 8 patients on blue foil wrapped KEMRON® (2 IU per dose) did very well. That single "blinded, placebo-controlled" report was the only report received from anyone regarding the thousands of lozenges sent to Kenya.

In the spring of 1990, the WHO (World Health Organization) wanted to test KEMRON®. The green foil wrapped lozenges were delivered to WHO for a quickly organized "multi-centre" clinical trial of 4 week's duration. One hundred eight (108) patients were treated in 5 different countries (Ivory Coast, Zimbabwe, Kenya, Cameroon, and Congo). The trial was designed to assess the patients after 2 and 4 weeks on "KEMRON®" treatments. The green foil wrapped lozenges were subsequently assayed at 183 IU of HuIFN-α per lozenge; the WHO patients all received that dose once daily dose for 4 consecutive weeks. The WHO reported to the press in May 1990 that the results were "inconclusive" and "did not replicate" the beneficial reports from Kenya. However, WHO's written report [38] actually reported that most of the initial clinical signs and symptoms (oral candidiasis, fatigue/weakness, appetite loss, insomnia, night sweats, dysphagia, cough, diarrhea, pruritus) were ameliorated by the end of the study in over 60% of the patients.

The American Foundation for AIDS Research (AmFAR) met to discuss oral IFN-α in the spring of 1990. It was decided to test KEMRON® independently at the Community Research Initiative - Toronto (CRIT). With some financial support from AmFAR, a cooperative Health Protection Branch of the Canadian Ministry of Health, and enthusiastic AIDS physicians in Toronto, a clinical trial was conducted in Canada One hundred fifty (150) men participated in the Canadian study. For 8 weeks, these men took either placebo, or 50 or 100 IU of HBL HuIFN-α daily. The benefits reported in Africa were not observed in the population treated in Canada [39]. Questions arose as to the dose and timing of administration of oral HBL HuIFN-α and the influences of race, gender, opportunistic infections and diet on the different studies. Why would black Africans respond differently from white Caucasians in Canada?

While the Canadian trial was in the planning stages, a call was received from the Institute of Noetic Sciences asking if they could test low-dose oral HBL HuIFN-α in cancer patients in Germany. Arrangements were made to deliver HBL HuIFN-α to Germany with the expectation that cancer patients would be treated. However, because of the "hype" out of Kenya about oral IFN-α and AIDS, Professor Gallmeier and his colleague Dr. Kaiser decided to use the lozenges on AIDS patients, instead of cancer patients. A study of 30 German patients was conducted for 12 weeks, 6 weeks on 200 IU IFN-α once daily and 6 weeks on placebo. The results were disappointing as the Germans did not respond as the Kenyan population was reported to respond. Only a transient (at 2 and 4 weeks, but not 6 weeks) improvement in CD4+ cell counts was noted [40]. Once again, a black African population responded differently from white Caucasians in Germany.

Other AIDS studies using oral IFN-α were conducted from 19891994 involving over 1000 patients. A study of 66 patients at Mahidol University in Bangkok tested placebo versus 100 or 200 IU of HBL HuIFN-α given daily for 24 weeks and reported a significant ($P < 0.05$) weight gain and relief of symptoms in AIDS patients given 200

IU of HBL HuIFN-α per day. Moreover, after 24 weeks, change in clinical complaints (P <0.02) and self-evaluation scores (P <0.01) were improved in AIDS patients given 200 IU of HBL HuIFN-α per day [41].

In a 24-week study, conducted at the Tropical Diseases Research Center in Ndola, Zambia, a total of 150 HIV-positive patients were treated with lozenges containing 150 IU of HBL HuIFN-α or a matching placebo [42]. One group of patients took active lozenges of IFN-α one week and placebo lozenges the next and alternated for 6 months. One group took IFN-α daily and one group took placebo daily. The treatment group that took 150 IU IFN-α lozenges daily experienced significantly (P<0.05) fewer HIV-related signs and opportunistic infections. The every-other-week IFN-α group had a significant (P < 0.02) improvement in the mean CD4+ cell count percentage compared to the placebo group. Both groups of IFN-α-treated patients tended to gain CD4+ cells while the CD4+ cell counts of the placebo group did not improve.

From these many studies, data accumulated and an IFN-α dose was chosen for the National Institutes of Health (NIH) oral IFN clinical trial (DATRI 022). A total of 560 AIDS patients were to be enrolled to three different sources of oral IFN-α versus placebo. In July 1995, the NIH ordered the clinical supplies for delivery to enroll patients. Unfortunately, because of slow enrollment, the study was halted in June 1998 and no meaningful results were possible. Because 560 patients were needed to provide sufficient "power" to analyze the data, there was objection to the publication [43] which drew conclusions based on too few patients.

The DATRI 022 study was designed to enroll 560 subjects to detect differences in treatments. It was reported [43] that only 247 evaluable study subjects were enrolled and data on CD4+ cell counts of 89 subjects who completed 24 weeks were presented. Therefore, 44.1% of the necessary number of subjects were enrolled and only 15.9% of the projected 560 subjects completed the study. The conclusion that these data "do not support claims of efficacy" for the measures studied therefore is invalid.

Lozenges containing 150 IU of HBL IFN-α were delivered so WHO could conduct a clinical trial of AIDS patients in Uganda. A total of 559 patients cooperated in the trial and were given either placebo or IFN-α daily for up to 6 months; however, the majority of the patients were treated for 30 days or less. Many patients died during the study due to diarrhea, tuberculosis and other complications associated with AIDS. Many patients had zero or very few CD4+ cells (mean baseline CD4+ cell count in HBL HuIFN-α-treatment group was only 60 CD4+ cells/ cu.mm) upon entry to the study thereby forecasting a probable early death. Indeed, nearly a third of the patients died during the study. Even under the severe circumstances of the WHO study, a CD4+ cell count improvement was noted for 18 weeks in IFN-α-treated patients. WHO published their negative conclusions [44]. Oral IFN-α benefits are most readily induced in patients with baseline CD4+ cell counts >200 treated for 6 months [45]. There is probably no single agent that will help AIDS patients with CD4+ cell counts of 60. Many of the patients in the WHO study entered with CD4+ cell counts of zero. It is not surprising that nearly 1/3 of the patients died.

Physicians in California who were members of Search Alliance set up a study to test their liquid oral IFN-α in AIDS patients but quickly became disillusioned with the results they saw. Within a few weeks, all the physicians abandoned the study, except Dr. Wilbert Jordan. Even though low-dose oral IFN-α therapy for AIDS patients was severely criticized, Dr. Jordan of Los Angeles continued using oral IFN-α; he reported beneficial effects [46, 47]. Dr. Jordan tested HBL IFN-α under a physician's IND (Investigational New Drug Application).

One group claiming oral IFN-α was ineffective treated only 8 patients with 15 IU HuIFN-α once daily for 6 weeks [48]. In contrast, other studies reporting a benefit used a dose of at least 150 IU IFN-α [36]. Two studies reported marginal benefits to oral HuIFN-α therapy. Patients (number = 41) with CD4+ cell counts from 100-350/cu.mm were given placebo or 150 IU natural oral IFN-α once daily for 6 weeks. After a 4-week rest, all patients could elect to take IFN-α for up to 48 addition weeks. The IFN-α did not affect CD4+ cell counts but appeared to improve symptomatology and delay progression to AIDS. The results were complicated because 24 of 41 of enrollees were also on azidothymidine (AZT) [49].

In Amarillo, 177 patients seropositive to HIV-1 were randomly enrolled to placebo or recombinant HuIFN-α 2a at 0.1, 1.0 or 10.0 IU/ pound body weight. This patient population was not cooperative as only 128/177 (72.9%) and 100/177 (42.9%) had recorded baseline body weights and CD4+ cell counts, respectively. The mean baseline CD4+ cell counts in 27 cooperating placebo patients was 421 and was 313, 407 and 314 in 25, 24 and 24 patients, respectively, given HuIFN-α 2a at 0.1, 1.0 or 10.0 IU/pound body weight (standard deviations similar-not shown). At 6 months, only 114/177 (64.4%) returned and at 12 months only 76/177 (42.9%) returned for evaluation. Despite the high drop-out rate and death loss of 18/177 (10.2%), the data suggested that the 1.0 IU dose of IFN-α may be beneficial [50].

AIDS Summary: Orally administered IFN-α has been tested in 23 studies of patients infected by HIV-1 [36]. The preponderance of data suggests that orally administered IFN-α is safe and useful in the management of opportunistic infections in HIV+ patients. AIDS is an epidemic still out of control in some parts of the world. The clinical efficacy observed with oral IFN-α in HIV+ patients, the ease of administration, lack of toxicity, room temperature stability and low cost indicate that oral IFN-α may have a role in helping manage AIDS.

Hepatitis. Millions of people – about 325 million worldwide in 2015 – are carriers of hepatitis B (257 million) or C (71 million) virus infections that can remain asymptomatic for decades. Each year it is estimated that 1.75 million people newly acquire hepatitis C virus infection. These people are at risk of slow progression to severe liver disease and death unless they receive timely testing and treatment. Unfortunately, access to affordable care is low [51].

Chronic infection with hepatitis C virus is the most common form of chronic viral hepatitis in the developed world [52]. Between 80 and 85% of those infected with hepatitis C go on to develop chronic infection [53]. In the US, hepatitis C virus infection is responsible for 40% of all chronic liver disease, 20-30% of all liver transplantation, and more than 8000 deaths annually [54].

Treatment of Hepatitis C with oral IFN-α. For many years, pegylated IFN-α therapy with ribavirin was the standard treatment for hepatitis C with clearance rates around 60%. In recent years, the advent of newer antivirals has seen the clearance rate dramatically improved. Here we review low-dose oral IFN-α studies which suggest an ancillary role in hepatitis treatment.

A preliminary human trial [55] was conducted with oral IFN-α to treat chronic hepatitis C. Doses of FN-α utilized were 150 IU or 300 IU given once daily for up to a year. Normalization of serum aminotransferase levels has been the most commonly utilized endpoint. Patients treated with IFN-α lozenges alone fail to achieve normalization of aminotransferases; however, significant decreases over time were seen, without side effects.

Perhaps the most intriguing finding was in a retrospective Japanese study (Hayashibara Biochemical Laboratories, 1993) in which 10 patients initially treated with 300 IU of IFN-α lozenges for 2-12 months (mean 6.2 months) were then placed on injectable IFN-α, 3 million units 3 times per week for a mean duration of 4.6 months (range 3-6 months). At the completion of the injection regimen, 8 of 10 patients had normalized serum aminotransferases. This response was sustained in 6 of the 8, and 1 additional patient achieved normalization during follow-up. Although the number of patients was small, this was a higher response rate than would be expected from initial high dose injectable IFN-α therapy. This raised the possibility that oral IFN-α had the ability to prime patients for greater responsiveness to injectable IFN-α and to induce more durable responses.

A clinical trial in Taiwan investigated the efficacy of oral HuIFN-α in preventing hepatitis C relapse. A total of 169 genotype 1b chronic hepatitis C patients, having achieved end-of-therapy virological clearance, were randomized to receive IFN-α lozenge 500 IU/ day (n=59), 1,500 IU/day (n=53), or placebo (n=57) for 24 weeks. Overall, no significant differences were found for the relapse rates in the 3 groups (P>0.05). However, in patients with fibroindex 1.4-1.7, relapse occurred in 1/12 (8.3%) 500 IU-treated group patients versus 9/21 (42.9%) patients of the other groups (P=0.05). In 158 patients receiving at least 4 weeks of oral IFN-α, significantly higher platelet count was found at the end of trial in the 500 IU group (P=0.003). In thrombocytopenic patients, a significantly expedited recovery of platelet counts were noted in the 500 IU treatment group (P=0.002). No drug-related severe adverse events were reported. In conclusion, at 500 IU/day, oral IFN-α exerted a borderline suppression effect of virological relapse in chronic hepatitis C patients with mild liver fibrosis. Additionally, oral IFN-α significantly expedited platelet count recovery after the end of pegylated IFN therapy [56].

Treatment of Hepatitis B with oral IFN-α. Among the estimated 257 million persons infected with hepatitis B virus worldwide, an estimated 27 million (10.5%) have been diagnosed and were aware of their infection in 2016. Only about 4.5 million have received hepatitis B virus treatment. Treatment coverage is low among all countries in all income strata [57]. Treatment with low-dose oral IFN-α is inexpensive and fits the health care budget of everyone.

Six studies in Poland, and a study in the Philippines reported that low-dose oral IFNα (usually a dose 100-200 IU daily) was safe and efficacious in treating hepatitis B. In Poland about half of IFNα-treated patients lost circulating hepatitis B e antigen (HBeAg) and hepatitis B DNA [58, 19, 59, 60, 61, 62]. In the Philippines, 36 patients were enrolled; half were given placebo and half were given 400 IU of oral IFN-α once daily for 8 months. Filipino IFN-α-treated patients had a significant ($P < 0.05$) clearance of HBeAg and development of antibodies against HBeAg [63]. A study in Japan reported that low-dose oral IFN-α (50-900 IU) was ineffective in treating 117 chronic hepatitis B patients [64]. The role of low dose oral IFN-α as complementary to the available vaccine needs further study.

Fibromyalgia. Although of unknown etiology, fibromyalgia is generally considered to be a post viral infection syndrome. Current treatment for fibromyalgia is usually antidepressants and painkillers. There is an immense loss of working hours in the US due to fibromyalgia, and a subsequently heavy financial burden to patients, employers and the government.

In a Phase II fibromyalgia study, low-dose oral IFN-α achieved excellent results in relieving patients from stiffness upon waking ("morning stiffness"). Patients reported feeling better than they had in years [65]. A confirmatory Phase II clinical study showed promising results. Patients participating in the study were divided into three groups, and each patient was given three lozenges per day. The three lozenges given to members of the first group contained 50 IU of HBL HuIFN-α each, the second group was given one 50 IU HBL HuIFN-α lozenge and two placebos, while members of the final group received three placebos. All three groups reported a reduction in morning stiffness, but across the entire study, the improvement was most pronounced in those taking one 50 IU lozenge of HBL HuIFN-α per day. However, the result did not reach statistical significance relative to the controls, nor did increasing the dose to three HBL HuIFN-α lozenges per day improve the results.

Participants were also given a low-dose of the anti-depressant drug, amitriptyline, which they began taking one month prior to the start of the IFN-α trial and continued throughout the three-month study. The addition of the amitriptyline was given so the placebo patients would not have to tolerate a four-month period without any beneficial therapy. However, use of amitriptyline complicated the analysis and interpretation of the study results. Patients who did not worsen during the first month's treatment with amitriptyline went on to demonstrate a significant (P=0.0035) reduction in morning stiffness (when they took the 50 IU HBL HuIFN-α lozenges once a day for three months, compared with placebo). However, those patients who reported worsening of their morning stiffness during the first month showed no benefit during the subsequent three months of HuIFN-α treatment [66]. Another modified Phase II study design might confirm the therapeutic benefit of low-dose oral HBL HuIFN-α in the treatment of morning stiffness in patients suffering from fibromyalgia.

Papillomavirus. When more than 20 HIV+ patients with oral warts were treated with low-dose HuIFN-α, regression of mouth warts, sometimes 100% regression, was noted in some of patients given IFN-α lozenges. Typically, oral warts in HIV+ patients warts grow, spread and enlarge monthly until the warts are a functional and cosmetic problem. Some patients need monthly "debulking" by surgery, freezing, or laser cautery because of the rapid growth of the warts. Spontaneous regression does not occur, presumably because of the faulty immune system of HIV+ subjects.

An open-label pilot study was conducted in which 15 HIVseropositive males (age 35-57 years) with multiple oral warts were enrolled [67]. All subjects were given combination anti-retroviral chemotherapy for at least 30 days before enrollment in this study. Chemotherapy in all subjects included at least one protease inhibitor (PI) and two nucleoside or non-nucleoside reverse transcriptase inhibitors. Subjects were treated with HBL HuIFN-α at 150 IU/day during weeks 0-8, and with 450 IU/day (150 IU three times per day[tid]) during weeks 8-16 delivered in the form of orally dissolved lozenges. At week 16, the number of warts and total surface area involved by warts were examined and compared to those determined at

baseline. In the subjects who showed an initial positive response, defined as 10% reduction in total surface area involved by warts, IFN-treatment was continued up to week 40. The protocol called for treatment to be discontinued in subjects who did not show positive response at week 16.

In practice, the investigator allowed any patient who desired it to remain on study up to week 40 given that no other effective treatment options existed. One patient was lost to follow-up after the baseline visit and was not included in the analysis. In the remaining 14 enrolled subjects, the mean total surface area (mm^2) involved by warts was reduced from 1010.5±1052.2 at baseline to 903.4±887.2 at week 8 and 827.2±643.4 at Week 16. One subject with an initial response (23% decrease in wart area) was lost to follow-up after week 8. At week 16, two subjects chose to discontinue treatment due to the lack of positive response. Another subject discontinued the study at week 16 for personal reasons despite a 45% decrease in wart area.

Ten subjects continued HBL HuIFN-α treatment beyond week 16, and 8 subjects completed the full 40-week treatment course. In these 8 patients, total surface area (mm^2) involved by warts was reduced from 1145.2±1377.9 at baseline to 282.8±381.2 at week 40 (P=0.11). Total number of warts was significantly (P=0.027) decreased in these 8 subjects from 20.4±11.1 at baseline to 9.0±6.9 at week 40. Two subjects dropped from treatment at weeks 32 and 36, respectively. Neither was a responder at the time of study withdrawal.

Among the 14 evaluable subjects, one showed complete response (100% clearance of all warts), 4 had partial response (>50% clearance), 2 had a minor response (>25% clearance), and 7 had no response. CD4+ cell counts and plasma viral loads determined at week 0, 16 and 40 did not show any significant changes.

Based on the results of the pilot trial, a blinded, dose-ranging study was conducted. A total of 21 HIV-seropositive subjects with multiple oral warts, who were receiving combination anti-retroviral therapy with or without PI, were enrolled in groups of 7 to one of three treatment arms: 450 IU, 900 IU, or 1,500 IU HBL IFN-α per day. Treatment was given initially for 16 weeks. In subjects showing evidence of response at week 16 (≥ 10.0% reduction in oral wart surface area), treatment was continued for 24 additional weeks. Subjects failing to show a response at week 16 were discontinued.

Due to business reasons, the study was halted prematurely, so not all subjects were able to complete a full treatment course. Nevertheless, a clear trend in favor of the HBL IFN-α 1,500 IU treatment arm was evident from this study. The same response criteria as in the pilot study were utilized, and the overall response rates by group were: • 450 IU: 0 complete, 1 partial, 2 minor and 4 non-responders

- 900 IU: 1 complete, 1 partial, 0 minor and 5 non-responders
- 1,500 IU: 2 complete, 3 partial, 0 minor and 2 non-responders

The second trial was a blinded, dose-ranging study in which 21 subjects were enrolled in groups of 7 to one of three active daily doses of IFN-α: 450, 900, or 1,500 IU. After 16 weeks of treatment, subjects were evaluated for initial response (≥10% reduction in wart area). Subjects meeting this response criterion were eligible for 24 additional weeks of treatment. Non-responders at week 16 were withdrawn from the study.

The majority of the adverse events reported in this trial were mild and self-limiting. No increased incidence or severity was noted at higher doses, compared to HBL HuIFN-α 450 IU. The most common adverse events in this study were: flu-like symptoms (5 subjects), and 2 subjects each with oral Candida and diarrhea.

Subsequent studies indicated that some oral warts regressed when HIV+ patients were given placebo. The "expert" opinion that oral warts do not regress, turned out to be incorrect and made more clinical studies in this indication less attractive. It has been observed that the 200 IU of IFN-α or 40 units of bovine IFN-α are safe and efficacious against anal warts and anal cancers [68].

Twenty women were given oral 150 IU HuIFN-α and 20 women were given placebo tid for 10 days to treat genital papillomavirus. At day 30 clearance of lesions occurred in about 70% of women given HuIFN-α compared to 18% of women given placebo. Most of the papillomaviruses typed were serotypes 6 and 11 [69]. In a similar study, HuIFN-α (12 women) or placebo (9 women) was given tid for 60 days. After 6 months, 9 women given HuIFN-α had a partial or complete response versus 3 women given placebo (P <0.005) [70].

In 14 women given oral HuIFN-α tid for 10 days, there was complete regression of cytopathic alterations and partial but not complete reduction in condyloma lesions after 30 days. In 15 women given placebo, there was no clinical improvement [71]. In a study of 25 women given oral HuIFN-α twice daily for 30 days versus 25 women given oral HuIFN-α and laser surgery for genital papilloma virus, the complete response was similar (59% versus 72%, respectively) [72]. In a group of 55 women with only laser surgery, 67% had a complete response. In another study of surgery combined with oral HuIFN-α (150 IU 2 or 3 times daily for 30 days), it was reported that HuIFN-α treatment did not influence the relapse rate in 90 patients at 6 months [73].

Measles. A Philippine study determined the safety and effectiveness of low-dose oral HuIFN-α against measles. A total of 30 confined pediatric patients were prospectively and randomly assigned to either a placebo or an oral IFN-α group and observed daily for 14 days in a double-blind manner. The IFN-α patients received a daily sublingual dose of 200 IU of lymphoblastoid HuIFN-α. The IFN-treated group showed shorter average duration of malaise (3.2 vs. 10.7 days, P< 0.0001), anorexia (3.1 vs. 6.7 days, P< 0.0001), and irritability (1.1 vs. 2.2 days, P< 0.01) and shorter duration of macular/maculopapular/papular lesions (4.3 vs. 8.2 days, (P< 0.0001) and branny desquamation (4.6 vs. 5.8 days, P> 0.05) and shorter time for rash to become generalized (5.5 vs. 10.3 days, P< 0.0001). No hematologic, renal, or liver toxicities were noted. The researchers concluded that low-dose oral HuIFN-α was both safe and effective in children with measles infections [74].

Respiratory Syncytial Virus (RSV). Recombinant HuIFN-α (10 IU/kg) or placebo was given once per day for 10 days to 38 hospitalized children in a double-blind study. Reduction in severity of disease, as measured by clinical score based on temperature, respiratory rate, apnea and wheezing, was significant (P<0.0001) in IFN-α-treated patients [75]. Over 2,000 children with RSV have been beneficially treated with oral IFN-α and adverse events were not noted [76].

Autoimmune Diseases

Sjögren's Syndrome. Sjögren's syndrome is a chronic autoimmune disorder characterized by dryness of the eyes and mouth. It can exist as a primary disorder or in association with other

autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and scleroderma. Patients with primary Sjögren's syndrome may have clinical signs such as rash, arthritis, pneumonitis and nephritis. Typical symptoms include the sensation of burning in the eyes, dryness of the mouth, skin, nose and vagina, difficulty swallowing, painful throat and fatigue. Oral candidiasis may also result from reduced saliva flow. Although Sjögren's syndrome is not life threatening, it can cause extreme discomfort and seriously impair quality of life.

Topical use of artificial tears is the prevailing treatment for the dry eye symptom of the disease. Artificial tears must be used on a regular basis. Intensive oral hygiene is prescribed to prevent progressive oral problems that may develop. Topical and systemic means of increasing salivary flow may provide transient relief of symptoms. Oral IFN-α therapy helps to relieve the dryness associated with Sjögren's syndrome, improves secretory function and may effectively supplement, or be used in lieu of, existing treatments.

Two 24-week Phase III clinical trials were conducted to test the use of HBL HuIFN-α lozenges in the treatment of primary Sjögren's syndrome. Results of both Phase III clinical trials demonstrated an improvement in saliva production in treated patients. The studies were double-blinded, placebo-controlled tests in which a total of 497 patients were treated tid for 24 weeks with lozengse containing either 150 IU HuIFN-α or placebo. Analysis of participants who completed the trials, designated as evaluable patients, found a significant increase in unstimulated whole saliva (UWS) production among the IFN-α treated patients, as compared to placebo [77]. Increases in UWS are important to the Sjögren's patient because UWS represents the basal salivary flow that is present over 90% of the day. Importantly, in IFNαtreated subjects, a significant correlation existed between increases in UWS and a decrease in the symptoms of Sjögren's syndrome, including oral dryness, throat dryness, nasal dryness and the ability to swallow foods. This research showed that patients perceived a benefit from having increased salivary flow.

The results of these studies were discussed with the FDA who said the demonstrated improvement in UWS flow was encouraging, but not sufficient for marketing approval as UWS was a secondary, rather than a primary study endpoint. The FDA suggested that an additional, largescale Phase III study be conducted that would include UWS flow as the primary endpoint. Because of the cost, the studies of this autoimmune disease ceased.

Behçet's Disease. Behçet's disease (BD) is a severe chronic relapsing autoimmune disorder marked by oral and genital ulcers, eye inflammation (uveitis) and skin lesions, as well as varying multisystem involvement including the joints, blood vessels, central nervous system, and gastrointestinal tract. The oral lesions are an invariable sign, occurring in all patients at some time in the disease. BD is found world-wide and is a significant cause of partial or total disability. The US patient population has been estimated as 15,000. The FDA office of Orphan Drugs granted orphan drug status for low-dose orally administered IFN-α treatment in this condition [78].

In Turkey, 84 (50 M, 24F) patients with BD were enrolled in a study of IFN-α lozenges versus placebo. Anecdotal evidence indicated that low-dose oral administration of IFN-α could be beneficial in the management of recurrent oral ulcers (OU). This double-blind, placebo-controlled study was initiated to explore the efficacy and safety of low doses of natural HuIFN-α administered as oral lozenges in the treatment of recurrent OU in patients with BD. Patients with BD and a history of recurrent OU for at least 1 year were enrolled at 4 treatment centers in Turkey. Patients exhibiting at least 2 OU with a total diameter of at least 4 mm were randomly allocated to daily treatment with either 2,000 IU IFN-α, 1,000 IU IFN-α, or placebo. Subjects were monitored weekly over an initial 4 weeks, and bi-weekly for another 8 weeks of treatment. OU were counted and measured at each study visit. The primary efficacy end point was the difference in the total OU burden at week 12 compared to that at week 0.

Of 84 randomized patients, 72 completed the trial. The drop-out rate was similar between the groups and there were no statistically significant differences between the groups with respect to the number of patients reporting an adverse event. There were no statistically significant differences between the treatment arms with respect to any of the efficacy endpoints [79]. While safety was confirmed, treatment with IFN-α lozenges (at the dosages tested) failed to reduce the total OU burden among BD patients from Turkey. Data developed over time indicate that either 2,000 IFN-α IU or 1,000 IFN-α is too high a dose. The dose that will help treat BD is probably 50 IU of IFN-α, not the higher doses tested in Turkey. Years after the study in Turkey, it was shown how critical it is to keep the dose of oral IFN-α very low to down regulate expression of autoimmune and inflammation genes [80]. Indeed, 15 BD patients in the US given low-dose natural bovine IFN-α reported clinical benefit. One woman in Tennessee and another woman in Kansas have used low-dose natural bovine or human IFNα for 18-20 years to manage BD [81].

Idiopathic Pulmonary Fibrosis. Idiopathic Pulmonary Fibrosis (IPF) is a chronic inflammatory fibrotic disorder localized to the lower respiratory tract and characterized by an alveolitis dominated by alveolar macrophages, polymorphonuclear leukocytes (PMNs) and, to a lesser extent, lymphocytes and eosinophils. The disease usually presents as dyspnea on exertion, the chest x-rays show diffuse reticulonodular infiltrates, and analysis of lung function reveals restrictive abnormalities. The disease process does not affect the upper or conducting airways, but bronchiolitis of respiratory bronchioles may be present and alveolar units are always involved.

Low-dose orally administered HuIFN-α was tested as a treatment for IPF under an Advanced Technology Program Grant awarded by the State of Texas to the Texas Tech University Health Sciences Center in Lubbock. The $100,000 grant was used by the Health Science Center to support a pilot study of 20 patients with IPF. A trial of low-dose, orally administered HuIFN-α (150 IU tid) showed minimal to no side effects. Subjects were evaluated with pulmonary function tests every 3 months and high resolution computed tomography (HRCT) at yearly intervals. Of the 9 subjects who completed at least one year, the forced vital capacity remained stable in 8 and the oxygen saturation after a 6-minute walk was stable in 7 and improved in one. One subject showing lack of progression was followed for over 5 years and another subject was followed for 3 years. The 8 subjects whose pulmonary function tests were stable showed no evidence of disease progression on HRCT scans. Five of 6 subjects who entered the study with a cough noted marked improvement within the first few weeks of treatment with corresponding increases in quality of life scores. These results [82] strongly suggest that this regimen can prevent progression according to the criteria defined in the International Consensus Statement published by the American Thoracic Society. A woman diagnosed with IPF 30

years ago died January 2018. A man diagnosed with IPF 12 years ago is still alive and both people attribute(d) their remarkable survival to low-dose oral IFN-α [80]. The low cost and safety of low-dose oral IFN-α makes it a reasonable chose for IPF patients.

Diabetes. A group of US medical researchers evaluated the safety and efficacy of ingested recombinant HuIFN-α for preservation of β-cell function in young patients with recent-onset type 1 diabetes. Subjects aged 3–25 years in whom type 1 diabetes was diagnosed within 6 weeks of enrollment were randomly assigned to receive ingested recombinant HuIFN-α at 5,000 or 30,000 units or placebo once daily for 1 year. The primary outcome was change in C-peptide secretion after a mixed meal. The conclusions showed that ingested HuIFN-α was safe at the doses used. In particular the 5,000-unit HuIFN-α treatment group maintained more β-cell function 1 year after study enrollment than individuals in the placebo group, whereas this effect was not observed in patients who received 30,000 units HuIFN-α. This study supports the idea that lower oral doses of HuIFN-α are more efficacious than high doses [83].

Multiple Sclerosis. Injected recombinant type I HuIFN beta (HuIFN-β) is licensed in the US to treat relapsing-remitting multiple sclerosis (RRMS). This high dose injected IFN-β regime decreases relapses, causes spontaneous in vitro IFN-γ production, reduces clinical progression, and decreases magnetic resonance imaging (MRI)-defined disease activity and lesions. Parenterally administered type I IFN use is, however limited by clinical and chemical toxicities, and the induction of antibodies that abrogate activity in vivo. Ingested HuIFN-α is nontoxic and has biological effects in humans. The ingested HuIFN-α showed no toxicity in normal volunteers or patients with RRMS at doses ranging from 300 to 100 000 units. In subjects with RRMS, a significant decrease in Con A-mediated proliferation and serum soluble intercellular adhesion molecule-I (sICAM-I), a surrogate measure for disease activity in multiple sclerosis, were reported. These studies again supported the oral use of HuIFN-α as a biological response modifier in humans [84].

Conclusions

There is a significant amount of evidence showing that low doses of HuIFN-α given orally can have significant benefits in cancers, viral illnesses and a range of autoimmune conditions. The reality is that very little of this available information has been translated into standard medical practice. The expiry of the major patents on type 1 IFNs has led to an expansion of their use in medicine. It is timely to re-examine oral administration of these IFNs, particularly at the more efficacious low doses.

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