REVIEW

Inosine Pranobex: A Key Player in the Game Against a Wide Range of Viral Infections and Non-Infectious Diseases

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ABSTRACT

Inosine pranobex (IP), commonly known as inosine acedoben dimepranol, isoprinosine and methisoprinol, has been proven to positively impact the host's immune system, by enhancing T-cell lymphocyte proliferation and activity of natural killer cells, increasing levels of pro-inflammatory cytokines, and thereby restoring deficient responses in immunosuppressed patients. At the same time, it has been shown that it can affect viral RNA levels and hence inhibit growth of several viruses. Due to its immunomodulatory and antiviral properties, and its safety profile, it has been widely used since 1971 against viral infections and diseases, among which subacute sclerosis panencephalitis, herpes simplex virus, human papilloma virus, human immunodeficiency virus, influenza and acute respiratory infections, cytomegalovirus and Epstein–Barr virus infections.

Following an analysis of almost five decades of scientific literature since its original approval, we here summarize in vivo and in vitro studies manifesting the means in which IP impacts the host's immune system. We also provide a synopsis of therapeutic trials in the majority of which IP was found to have a beneficial effect. Lastly, positive results from limited studies, suggesting the putative future use of IP in new therapeutic indications are briefly described. In order to support use of IP against viral infections apart from those already approved, and to establish its use in clinical practice, further well-designed and executed trials are warranted.
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INTRODUCTION

Inosine pranobex (IP), commonly known as inosine acedoben dimepranol, isoprinosine or methisoprinol, is a synthetic compound of the p-acetamido-benzoate salt of *N–N* dimethylamino-2-propanol with inosine in a 3:1 molar ratio, with immunomodulatory and antiviral properties. The drug was initially authorised in 1971 and is currently marketed in more than 70 countries worldwide for the treatment of viral

diseases, including subacute sclerosing panencephalitis (SSPE), herpes simplex virus (HSV) and varicella infections, human papilloma virus (HPV), cytomegalovirus and Epstein–Barr virus infections, acute viral respiratory infections, measles, and immunosuppressed states.

Results from numerous studies as early as the 1970s and 1980s suggested beneficial effects of treatment with IP in several diseases and infections, among which were HSV infections, SSPE, genital warts, influenza, etc. To date, it is uniformly supported that IP is a drug which is well tolerated and free from serious side effects. This fact is supported both by the small number of adverse reactions and the limited number of subjects withdrawn from clinical trials, as well as available post-marketing exposure data from patients treated with IP. In long-term treatments and large doses, transient nausea may occur [1]. A transient rise of serum and urinary uric acid concentrations, owing to inosine metabolism, is the most commonly reported side effect and is more pronounced in males. Nevertheless, hyperuricemia was found to be generally reversible [1–4]. Based on results from cytotoxic assays, comet and micronucleus assay, and Ames testing, it was concluded that IP is neither cytotoxic, genotoxic nor mutagenic [5–8].

IP's antiviral and antitumor activities have been demonstrated both in vitro and in vivo and are considered secondary to an immunomodulating effect; nevertheless, the exact mechanism of action is not yet clearly defined. The occurrence of drug-resistant viral strains against traditional antiviral agents underlines the need to further exploit the respective properties of IP, in order to expand the existing arsenal against viral diseases. IP continues to be the subject of various clinical and non-clinical studies. Its efficacy, either as monotherapy or as part of a combination therapy, has been re-visited for various diseases. Moreover, new, potentially therapeutic indications for IP or new agents for concomitant administration have been investigated.

We here present a synopsis of in vitro and in vivo studies which support the immunomodulatory and antiviral properties of IP, and, consequently, unveil its pleiotropic mode of action and justify its beneficial effect on various diseases and infections, as exemplified in multiple therapeutic trials.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

MECHANISM OF ACTION

For decades now, IP has been a widely used drug due to its immunomodulatory and antiviral properties, and several mechanisms of action have been postulated in an effort to explain these properties. Studies have shown that IP can impact both the humoral as well as the cell-mediated aspects of the immune system, in such a way that it enhances the host immune responses and can also exhibit antiviral effects considered secondary to this immunopotentiation.

Administration of IP apparently induces a Th1 cell-type response, evidenced by an increase in the levels of pro-inflammatory cytokines (e.g., IL-2, IFN-γ), both in vivo and in vitro, in mitogen- or antigen-activated cells [9–12]. This response initiates T-lymphocyte maturation and differentiation and potentiates induced lymphoproliferative responses [10–13]. It has been reported that IFN-γ inhibits production of IL-10 [14], which, in combination with the drug-induced decrease in the production of IL-10 and other anti-inflammatory cytokines, suggests that IP could modulate the suppressive effect of these cytokines on innate and adaptive immunity. IP's potential against viral infections is also supported by the increase in natural killer (NK) cells population and increased NK activity [12, 13, 15–19]. Neutrophil, monocyte and macrophage chemotaxis and phagocytosis are also potentiated by IP [12, 13, 20], while NK activity of eosinophils is enhanced due to an increase of the number of lgG and complement surface markers triggered by IP administration [21].

The humoral immune response is mainly increased by stimulation of B lymphocyte differentiation into plasma cells and the enhancement of antibody production [22, 23].

In an attempt to explain the antiviral properties of IP, various hypotheses have been

formed. The in vivo antiviral activity of IP is believed to result from an enhancement of host immune responses due to the drug [20]. In that view, the drug augments immunological processes by lymphocytes once they have been triggered by viral antigens, as it is not able to stimulate resting lymphocytes by itself [10, 20, 22, 24]. Notwithstanding, there may be other possible modes of action.

IP has been found to stimulate a nonspecific immune response, independent of the specific viral antigen [6], which presumably indicates that its viral inhibitory effects can also be placed on the level of transcription and translation. In fact, on one hand, cellular RNA and protein synthesis are markedly depressed shortly after viral infection, and on the other hand, IP enhances host cell RNA and synthesis and decreases viral RNA synthesis [22, 25].

It has been suggested that one of the drug components or even the drug complex itself links to the ribosomes of the infected cells, provoking a steric modification of host ribosomal structure, thus providing an advantage to host cellular RNA over viral RNA in the competition for linkage with the ribosomal combining sites [25]. The consequence would be a non-reading or incorrect reading of the viral genome, with incorrect transcription of the viral genetic code [26].

Another hypothesis is based on the rapid metabolism of IP and the inhibitory role of inosine. It was assumed that, prior to its metabolization, IP is dissociated into its constituents, i.e., three molecules of N–N dimethylamino-2-propanol-p-acetamidobenzoate and one molecule of inosine, of which the latter inhibits the synthesis of the phosphoribosyl pyrophosphate, an intermediate in the biosynthesis of purine nucleotides such as adenylate and guanylate. Since IP inhibits the conversion of ribose phosphate to phosphoribosyl pyrophosphate, it may act by blocking the synthesis of viral RNA, as this process is faster than cellular RNA synthesis [27].

In light of a new study unveiling inosine's ability to cause ribosome stalling and context-dependent decoding during translation (to either adenosine or uracil) [28], more focus should be placed on the impact of IP at the transcriptional and translational level, in order to fully elucidate its mode of action in viral replication.

Based on the described IP effects and hypotheses, we can conclude that its action remains elusive, but undoubtedly pleiotropic. Overall, the drug may act to restore depressed T-lymphocyte function to normal by increasing lymphokine production, or alternatively by increasing cell ribosomal RNA and protein synthesis while simultaneously inhibiting the use of cell ribosomal RNA for viral replication. The in vivo and in vitro studies exhibiting immunomodulatory and antiviral properties of IP are outlined in the following sections.

IMMUNOMODULATING ACTIVITY

Early in vivo and in vitro studies on the immunomodulating activity of IP, dating roughly back to the first two decades of its use, have been presented in various review papers [1, 8, 29–32]. We here summarize the main findings from these studies together with results from more recent publications which may shed further light on the pharmacological activity of IP (Table 1).

The impact of IP on Th1- and Th2-related cytokines has been investigated in vitro both in human and animal cells. Levels of studied cytokines remained unchanged in resting lymphocytes, incubated with IP. In contrast, IP has been reported to increase the production of IL-2, interferon-gamma (IFN-γ) and tumor necrosis alpha (TNF-α), and to decrease the production of IL-4, IL-5 and IL-10, in mitogen-stimulated cells [10–12].

In vitro, IP appeared to improve or restore the impaired chemotaxis and phagocytosis of neutrophils [12]. In patients with parasitic infections, exposure to IP increased the receptors for the Fc fragment of IgG and for C3 of eosinophils and enhanced their killer functions against nucleated target cells [21].

B lymphocyte differentiation may be promoted by IP, but the effect of the drug on B cells may result from its effect on macrophage or T-helper cells [33]. Additionally, the drug induced an early chromatin activation in peripheral blood mononuclear cells from patients with the acquired immunodeficiency syndrome (AIDS)-related complex (ARC) [34].

Table 1 In vitro effects of IP on immune responses

Population[a]	IP (μg/mL)	IL-1	IL-2	IL-10	TNF-α	IFN-γ	Lymphocytes (blastogenesis)	NK	Comments	References
HS	0.1–200	↑	↑	→	↑	↑	↑	↑	No effect on Ig synthesis	[10, 15, 16, 109–111]
Aging patients	100	na	↑	na	na	na	↑	↑	Neutrophil chemotaxis was restored to normal	[12]
RA	0.5–25	na	↑	na	na	na	↑	na	No effect on Ig synthesis	[109]
SLE	0.5–25	na	↑	na	na	na	↑	na	Restored the typically high Ig synthesis by SLE lymphocytes	[109]
HIV/AIDS/ARC	100	↑	↑	na	na	na	↑	na	IP treatment restored: IL-1, IL-2 to normal or near normal levels impaired T-helper cells	[33, 44, 111, 112]
Uremic patients	100	na	–	na	na	na	↑	↑	IL-2 production was not enhanced by IP	[113]
Cancer	2–200	↑	↑	na	na	na	↑	↑	Monocyte chemotaxis was restored to normal or near normal levels	[13, 19, 114, 115]

ARC AIDS-related complexes, HS healthy subjects, IP inosine pranobex, na not available, RA rheumatoid arthritis, SLE systemic lupus erythematosus

[a] Studies on peripheral blood mononuclear cells. Effects of mitogen-activated cells were enhanced by IP; no effect in resting lymphocytes

Several mediators of immune function were stimulated by IP and the upregulation of the host protective Th1 cells in parallel with the downregulation of Th2 cells was evidenced in vivo in various experimental animal models [11, 35]. In vitro production of IFN-γ was significantly increased in murine lymphocytes, as opposed to IL-3 and IL-4, and there was no effect on NK cells or on antibody-dependent cellular cytotoxicity [20, 35]. In an experimental mouse model of the Epstein–Barr virus, a 14-day treatment with IP resulted in an increased number of leukocytes, an increased percentage of neutrophils, and a reduced number of atypical lymphocytes [36].

Pharmacodynamic, in vivo studies in healthy subjects are rather limited. The serum levels of certain cytokines during and after IP treatment were determined in 10 healthy volunteers with a mean age of 41 years, to whom 1 g of IP was administered thrice daily, for 3 weeks (5 consecutive days weekly). An increase in the proinflammatory cytokines was observed, while fluctuations of cytokine levels were found to correlate with the treatment scheme applied [9]. Daily administration of 4 g of IP in 21 healthy individuals resulted in a rapid response in a high percentage of participants, an increase in the number of lymphocytes and a circadian fluctuation of them in the peripheral blood [37]. An early rise in NK cells (as a percentage of total peripheral blood lymphocytes), maintained at the termination of the study was observed in 10 healthy volunteers, to whom 4 g of IP were administered daily for 14 days [15].

Various studies have focused on the effect of IP on the immune system of patients affected by different diseases. In patients with herpes virus infection, higher lymphocyte transformation was observed in treated individuals than in the control group [38]. In patients with autoimmune diseases, like aphthous stomatitis or alopecia, IP was found to increase the number of active T-cell rosettes and enhanced responses to mitogen activation [39–41]. A similar increase, a renewal in depleted T-cells and seroconversion to anti-HBe was achieved in patients with chronic active hepatitis B [42, 43]. Patients with persistent generalised lymphadenopathy (PGL) or ARC exhibited

significant increase in the number of NK cells and NK activity, which lasted up to 5 months after cessation of IP [18]. Treatment with IP also resulted in enhanced NK cell activity as well as increased numbers of CD4+T-helper cells in clinically improved patients with chronic fatigue syndrome (CFS) [17].

In summary, IP potentiates or enhances immunological events (e.g., production of cytokines, differentiation of cells of the T-lymphocyte lineage) initiated by other triggering agents such as mitogens, antigens, phagocytic stimuli or lymphokines. The impact of IP on NK cells and NK activity has also been demonstrated.

ANTIVIRAL ACTIVITY

The production of effective antiviral drugs is in general a difficult and time-consuming process, and the emergence of resistant strains owing to extended use of antiviral drugs, is a key issue in the development of novel antivirals, as for example in the case of herpes infections. A useful strategy would be to optimize the efficacy and selectivity of existing antiviral drugs by combining them with other well-known agents that could potentiate their effect.

The antiviral effect of IP has been extensively reviewed by Campoli-Richards et al. [31], and found to be modest and inconsistent in standard tissue cultures. IP was successful in inhibiting the replication of several RNA and DNA viruses, among which are HSV, cytomegalovirus, LAV/HTLV-III virus, adenovirus 10, vaccinia virus, polio virus, influenza types A and B viruses, rhinovirus, rabies virus, viral encephalomyocarditis, enteric cytopathic human orphan virus and eastern equine encephalitis virus. In contrast, a lack of efficacy has been noted for parainfluenza virus, measles virus, mumps virus, rhinovirus and western equine encephalitis virus [31].

To date, there has been an ongoing in vitro investigation of the antiviral properties of IP on new target viruses, as well as on different strains of already studied viruses. IP has been found to possesses a weak anti-HIV-1 activity in human peripheral blood mononuclear cells [44].

Inhibition of viral RNA synthesis was achieved at a concentration of 1 mg/mL IP at 72 h after infection of MA-104 cells with the simian rotavirus strain SA-11 [27]. In a recent study, IP was found to strongly inhibit the multiplication of adenoviruses (HAdV-2 and HAdV-5), in particular in combination with IFN-α [45].

No vaccine is currently available to prevent herpes infections. Acyclovir is the first selective inhibitor of alphaherpesviruses and consequently is the treatment of choice for HSV-1 and HSV-2 infections. However, the high prevalence of HSV strains with reduced susceptibility to acyclovir in immunocompromised patients [46] and the low oral bioavailability and adverse effects of the second line treatments (e.g., foscarnet, cidofovir) underline the need for new antiviral agents. In that perspective, Majewska et al. [5] focused on the in vitro inhibition of the replication of HSV-1 strains by IP and IFN-α, and investigated whether there is an HSV-1 strain-specific pattern for the action of these compounds. The degree of inhibition of viral replication in vitro depended on the cell line and examined strain. Overall, increasing concentrations of IP (50–400 μg/mL) produced progressively growing inhibitory effects on HSV-1 replication in different cell lines, while a combination of IP and IFN-α displayed higher efficacy than either treatment alone [5].

The antiviral activity of IP was also studied in several in vivo experimental animal models of infection, such as influenza virus and herpes virus [20, 31]. A marked increase in the survival rate of the animals was observed.

THERAPEUTIC TRIALS

To date, several therapeutic trials with IP have been designed for various infections and diseases, among which herpes infections, SSPE, HIV infections, AIDS and PGL, type B and C viral hepatitis, HPV infections and autoimmune diseases. The drug has been compared with placebo in several cases or versus other available treatments. The usual oral daily dosage of IP has ranged from 25 to 100 mg/kg, totalling 1–6 g, in single or divided doses (4–6).

Herpes Virus Infections

Human HSV types 1 and 2, commonly known as HSV-1 and HSV-2, belong to the Alphaherpesvirinae subfamily of AIDS Herpesviridae family. HSV-1 usually causes orofacial infection, whereas HSV-2 is transmitted mainly sexually and is more often associated with genital infection. However, HSV-1 is an increasing cause of genital infection [47, 48]. Both viruses can establish latent infection and there can be a recurrence affecting the same dermatome.

HSV-1, transmitted primarily by oral–oral contact, causes orolabial herpes ("cold sores") in those infected. HSV-1 infections occur principally during childhood and they are not eliminated from the human body. HSV-1 is the most common identified causal agent of sporadic encephalitis in children and adults. For 2012, the average worldwide prevalence of HSV-1 infection was estimated to be 67%, while there was approximately a total of 118 million new infections reported [48].

The clinical presentation of HSV-2 infection is variable, and the majority of individuals are unaware that they are infected. In 2012, worldwide estimated prevalence and incidence of HSV-2 infection were 11.3 and 0.5%, respectively. Affected people had an age range of 15–49 years, and more than half were women [49]. Although rare, infection in the neonate is associated with a high risk of severe morbidity and mortality [50].

Several double-blind, placebo-controlled studies of IP in herpes infections (labialis or genitalis) and other types of herpetic infections, such as zoster, have shown encouraging results which are summarized in Table 2.

In a recent study by You et al. [3], the efficacy and safety of oral IP was compared with acyclovir in the treatment of recurrent herpes labialis (RHL) and recurrent herpes genitalis (RHG). IP was as equally effective as acyclovir in treating RHL and RHG with significantly greater reduction of the short-term recurrence rate of herpes genitalis at 3-month follow-up. The main limitations of this study are the single follow-up at 3 months after treatment discontinuation, which cannot reflect the long-term

Table 2 Summary of studies investigating the clinical efficiency of IP in alphaherpesvirus infections

Infection	Treatment	Dose regimen	Treatment duration	Follow-up	No. of patients [controls]	Age (years)	Main findings	References
Herpes labialis	RHL IP	70 mg/kg/day	5 days/week 5th, 9th, 12th weeks	12 months	23 [16]	25 ± 7	12 months after beginning of the trial, fewer recurrences in 30% of treated patients	[116, 117]
	PHL IP	1 g, qid	7 days	–	143 [168]	na	Clinical response highly significantly in patients with both primary lesions or recurrent episodes treated with IP	[118]
	RHL IP	1 g, qid	7 days	–	261 [240]	na	Better overall response in IP treated patients than placebo, irrespective of the stage of the lesion on presentation. Mean reduction in TSS (based on pain, itching and inflammation) was significantly greater in IP group. Fewer new lesions developed in IP group	
	RHL (I) ACV (II) IP	ACV: 200 mg, 5 times/day IP: 1 g, qid	7 days	3 months	69 (50 F, 19 M) [68]	40.93 ± 11.50	No difference in TSS between Group I and Group II on the 3rd or 7th day of treatment. No difference in the efficacy rates between the two groups	[3]
Herpes genitalis	PHG IP	4 g/day	12 days	–	19 [20]	na	Significant differences in healing rates between IP and control. Treated patients: shorter duration of itching, tender adenopathy, time to healing of lesions, duration of viral shedding from genital lesions after onset of therapy	[38]
	RHG IP	70 mg/kg/day	5 days/week 5th, 9th, 12th weeks	12 months	15 [16]	25 ± 7	Fewer recurrences for treated RHG but not controls. IP prolongs time of recurrence in 30% of patients	[116, 117]
	PHG IP	1 g, qid	7 days	–	35 [29]	na	Overall clinical response: on day 7, in favour of IP both in PHG and RHG	[119]
	RHG IP	1 g, qid	7 days	–	23 [26]	na	Mean reduction in TSS greater in treated patients (PHG + RHG). More lesions healed, less new lesions reported for the treated group	
	RHG (I) Episodic treatment (II) Continuous treatment (III) After 6 m, IP for 6 m	3–4 g/day during recurrent episodes (M: 1 g qid, F: 1 g tid)	(I) During each recurrence, up to 4 episodes (II) Between recurrences 1 g/day, 6 months	–	64 (24 F, 40 M) [62] 26 [4 F, 22 M]	32.5 ± 8.5 34.3 ± 9.5	Continuous administration of a relatively low dose of IP with higher doses during recurrences produces a significant reduction in the RR of genital HSV infections. Further reduction in RR after crossing over from placebo to IP for a further 6 months	[120]
	RHG (I) ACV (II) IP	ACV: 200 mg qid IP: 1 g qid	12 weeks	6 months	14 (5 F, 9 M) 17 (11 F, 6 M)	34.2 ± 6.8 32.3 ± 6.8	In Group I (vs.. Group II): time to 1st recurrence significantly longer frequency of recurrences significantly. After cessation of treatment: similar mean frequency of recurrences in two groups	[121]

Table 2 continued

Infection	Treatment	Dose regimen	Treatment duration	Follow-up	No. of patients [controls]	Age (years)	Main findings	References
RHG	(I) ACV (II) IP	ACV: 400 mg bid IP: 500 mg bid	24 weeks	24 weeks	(I) 49 (41% F, 59% M) (II) 53 (31% F, 69% M) [25]	(I) 35.7 ± 10.4 (II) 33.5 ± 8.3	In Group I (vs. Group II): lower proportion of recurrences. Reduced mean number of reported recurrences per patient. Shorter mean duration of breakthrough lesions. Longer mean time to 1st recurrence. No difference of mean time to 1st recurrence after treatment cessation	[122]
RHG	(I) ACV (II) IP	ACV: 200 mg, 5 times/day IP: 1 g qid	5 days	3 months	69 (24 F, 45 M) [69]	37.23 ± 9.43	At 3-month follow-up: greater reduction of the short-term recurrence rate of herpes genitalis	[3]
Herpes zoster	IP	500 mg q3 h	4 days	–	6 [7]	9.5	No discernible therapeutic effects in children with cancer	[123]
	IP	50 mg/kg/day	5 days	30 days	18 (11 F, 7 M) [18]	57.4 ± 20.6	In treated group: significantly better improvement of skin lesions. Enhanced reduction of pain. Healing of lesions faster in patients treated < 5th day of disease	[124]
	(I) GRF (II) IP (III) GRF + IP	(I) 125 mg qid (II) 1 g qid	30 days	30 days	(I) 7 (6 F, 1 M) (II) 20 (10 F, 10 M) (III) 20 (6 F, 4 M) [10]	(I) 67 ± 6.45 (II) 66 ± 3.17 (III) 63 ± 3.86	(II) Significant acceleration in drying of vesicles and reduction of pain (I) + (II). Significantly more effective reduction in pain vs.. (I)	[125]
	IP	2 × 500 mg, bid or qid	6 days	3 months	21 (11 F, 10 M) [17]	61–91	IP neither shortened acute phase of HZ nor PHN. No influence of the natural history of HZ in the elderly	[126]

ACV acyclovir, bid twice/day, GRF griseofulvin, HZ herpes zoster, IP inosine pranobex, na not available, q3h every three hours, qid 4 times a day, PHG primary herpes genitalis, PHL primary herpes labialis, PHN prevented postherpetic neuralgia, RHG recurrent herpes genitalis, RHL recurrent herpes labialis, RR recurrence rates, TSS total symptom score

recurrence rate of RHG, and the lack of a control group with placebo treatment.

Subacute Sclerosing Panencephalitis (SSPE)

SSPE is a progressive and fatal neurodegenerative encephalitis owing to infection by the measles virus and its persistence in the cerebral nervous system. The prevalence of SSPE is inversely connected to measles vaccination and dependent on the patient's age. The estimated incidence of SSPE ranges from 4 to 11 cases per 100,000 cases of measles and involves mostly children younger than 5 years old [51, 52]. There is an average of 4–10 years between the measles infection and the onset of the disorder, and prevalence is higher in males [53].

Several case reports have suggested that IP may provide beneficial therapeutic effects in patients with SSPE (reviewed in Campoli-Richards et al. [31]; Gadoth [54]) contrary to Noetzel and Dodson [55] who reported unabated progression of cerebral pathology in a patient with SSPE despite continuous treatment with IP (70 mg/kg/day) and periods of considerable clinical improvement or stabilization. In another case report, improvement was observed after a combination of IFN-α, ribavirin and IP therapy between 6 and 10 months; however, the patient suddenly deteriorated, and died [56].

Long-term studies, with or without a control group, have tested the impact of IP as a monotherapy in SSPE patients. Moreover, combined treatment regimens including IP were compared between them and against controls as to their effects in SSPE (Table 3). In most of the studies, it was suggested that the drug both increased survival and decreased neurological deficiencies [57–61].

The combination of IP and IFN-α appeared to be an effective treatment of SSPE (Table 3). In general, the beneficial effect of this combined regimen was observed in patients with slowly progressive SSPE, in contrast to patients with an acutely progressive course. Differences between studies could be attributed to the natural history of the disease, the disease stage at the time

of IFN-α administration, the scope of each study, the limited number of patients, the use of historical controls, and the duration of treatment and of follow-up. Albeit with limited data, IFN-β has been suggested as an alternative to IFN-α, due to fewer side effects and an easier route of administration [62, 63].

Various other kinds of drugs, such as amantadine, antivirals and DNA polymerase inhibitors [64–67], have been tested for treatment or to control disease progression. The efficacy of IFN-α, amantadine, and IP in the treatment of SSPE was compared and all three drugs were found to be relatively effective in either ceasing or slowing down progression of the disease. Nonetheless, the efficacy of IP outweighed that of amantadine and IFN-α by an order of four and two, respectively [65]. Patients were also found to benefit from either the combination of IP with IFN and lamivudine [67] or with IFN and antivirals [66].

The results from a multinational survey on actual diagnostics and treatment of SSPE, incorporating the experience of contributing physicians, revealed that IP monotherapy and combined oral IP plus ribavirin were applied frequently, as opposed to any combinations of IP with the following: IFN-α either subcutaneously or via an implanted pump, ribavirin plus IFN-α via an implanted pump, intraventricular IFN-α plus ribavirin, amantadine, and subcutaneous IFN-β [68]. Clinical and demographics characteristics along with commonly applied treatments were reviewed in a retrospective study including 43 children. IP was apparently the mainstay treatment either as a monotherapy (51% of patients) or in combination with IFN-β (4.7%) [69].

No cure exists for SSPE, which can only be prevented by a timely vaccination against measles. Nevertheless, the efficacy of IP on disease progression and patient survival rate, especially at early stages of SSPE, is evident by the obtained results (Table 3). Combined administration of IP and interferons has been supported by the majority of studies to achieve clinical improvement and prolonged survival. It should be noted that treatment shorter than 2 months was not found to be effective, and

Table 3 Clinical studies of the effectiveness of IP (monotherapy or in combination) in subacute sclerosing panencephalitis treatment

Treatment	Dose regimen	Treatment duration	Follow-up period	No. of patients [controls]	Age (years)	Main findings	References
IP	100 mg/kg/day (5 doses, 3–5 g/day)	Not < 3 months Up to 4 years	–	15 (7F, 8 M)	8.5–18[e]	Remission: 44%, sustained for more than 2 years within 9 months of IP administration (33%) Transient improvement followed by deterioration: 20% Stability then deterioration: 3% No evidence of benefit/acceleration of symptoms: 33%	[57]
	100 mg/kg/day (q6h)	Minimum 1 year	Up to 3 years	6 (2 F,4 M)	7–17	Clinical condition of 1 improved minimally 1 remained unchanged, 4 continued to deteriorate	[58]
	50–100 mg/kg/day (q2 h-tid, 1.5–6 g)	2–25 weeks	–	18 (3 F, 15 M) [96]	7–16	No statistically significant difference in recovery rate of in treated vs. control Improvements in clinical course unlikely associated to IP	[60]
	100 mg/kg/day (dd)	15 months–7 years	Up to 4.5 years	12 (5 F,7 M) [15 HC]	5–17[a,e]	Onset of SSPE, 21 months: no difference between groups 2–4.5 years: NDI (IP) ≪ NDI (HC) More pronounced difference in the slowly progressing SSPE group No difference in the rapidly developing group	[59]
	100 mg/kg/day (q4h)	<1 month up to 9.5 years	Up to 9.5 years	98 (35 F, 63 M) [163 HC]	8 months–26.2 years	IP prolongs life in patients with SSPE Survival probability (> 6 years): 62% (IP) vs. 6–26% (HC)	[61]

Table 3 continued

Treatment	Dose regimen	Treatment duration	Follow-up period	No. of patients [controls]	Age (years)	Main findings	References
(I) IP + PG-45 (II) IP + TFX (III) IP	IP: 6–8 tab × 500 mg (dd, 3–4 g/day), PG-45: 3–4 mg (once/month) TFX: 10 mg/day, 2 months	6 months	–	15 (9 F, 6 M) 14 (5 F, 9 M) 11 (5 F, 6 M)	9–23 8–19 6–16	Improvement/stabilization/zztationary: Group I (60%) > Group II (42.9) > Group III (18.2%) Progression: Group III (45.5%) < Group I (20%) < Group II (15%) Deterioration/death: Group III (81.8%) > Group II (57.1%) > Group I (40%)	[66]
IP + IFN-α	IP: 100 mg/kg/day	3–60 months	2–54 months (from IFN cessation)	22 (7 F, 15 M) [77 HC]	8–17	Decrease in NDI: 50% Stability: 22.7% Decrease progression rate: 13.6% Remission rate: 50% (IP + IFN) vs.. 11.6% (HC)	[127]
IP + IFN-α 2b	IP: 100 mg/kg/day (2 dd) IFN: 10^5–3×10^6 U, biw	na	12–40 months	18 (2 F, 16 M) [11 HC]	5–14	Remission/improvement: 44% (IP + IFN) vs. 9% (HC) vs. 5% (literature) Deterioration/.eath: 56%	[128]
IP + IFN-α	IP: 50–100 mg/kg/day	na	56–108 months	22 (7 F, 15 M) [35 SSPE][c]	8–17	Survival rate (IP + IFN) > Controls Initial improvement/stabilization: 16/22 (73%) Of these 16 patients: deterioration in 8, 4 died, 6–90 months after treatment	[129]

Table 3 continued

Treatment	Dose regimen	Treatment duration	Follow-up period	No. of patients [controls]	Age (years)	Main findings	References
(I) IP vs. (II) IP + IFN-α 2b	IP: 50–100 mg/kg/day IFN: 10^5–10^6 U/m²/day, 5 days/week	IP: IFN: 2- to 6-month intervals, up to 6 times	3–4 years	4 (M) 4 (M)	18–22	(I): 1 patient died and 3 patients deteriorated (II): 1 patient showed remission, 2 stabilized, 1 mildly deteriorated	[130]
(I) IP vs. (II) IP + IFN-α 2b	IP: 100 mg/kg/day (3dd, max 3 g/day) IFN: 10^5–10^6 U/m²/day	IP: 6 months IFN: 6 m	2 years	39 28	3–22	Improvement rates/mortality: no statistically significant differences among Group I/II. Higher in groups I + II (∼ 35%) vs. literature (5–10%)	[108]
(I) IP vs. (II) IP + IFN-α	IP: 50–100 mg/kg/day IFN: 10^5–10^6 U/m²/day	IP: IFN: 5 days/week, 6-week courses, 2- to 6-month intervals (max. 6 times)	16–160 months	9 (M) 10 (1F, 9 M)	18–22	(I) 1 patient showed progression, 1 stabilization, 7 died (II) 1 patient showed progression, 2 stabilization, 7 died IP or IP + IFN did not change the prognosis in long-term follow-up periods	[131]
IP + IFN-β	na	2–15 months	–	7 (2 F, 5 M)	6–21	Improvement was observed in 3 patients, stabilization in 2, disease progression/death in 3. Treatment < 2 months was not effective	[63]

Table 3 continued

Treatment	Dose regimen	Treatment duration	Follow-up period	No. of patients [controls]	Age (years)	Main findings	References
(I) IP + IFN-β1a (II) IP + IFN-β1a	IP: 50–100 mg/kg/day IFN (I): 60 μg, qw IFN (II): 22 μg, tiw	At least 3 months	1 year	38 (13 F, 25 M) 19 (5 F, 14 M)	6.1 6.3 (mean)	Survival and clinical response rates of the disease higher in Group II than Group I	[62]
IP + IFN-α2a +3TC	IP: 100 mg/kg/day (2–3 dd) IFN: 10 rnU/m^2, tiw 3TC:10 mg/kg/day, bid	IP + 3TC started after IFN cessation IFN: 6 months	7–28 months	19 (7 F, 12 M) [13]	2.5–13.5	Remission rate: 36.8% (treatment) vs. 0% (control) vs. literature (5%) Mortality rates Mean survival period longer in treated than in control	[67]
IP^d	IP: < 50– >100 mg/kg/day	na	–	89 (33 F, 56 M) [62 HC]	9.3^e	Survival rates/prolonged remission: IP ≫ control Progression: slower in IP, or IP + IFN than control Considerably or moderately favorable course: with IP 26.1% of patients treated with < 50 mg/kg/day 35.7% of those with ≥ 50 and < 100 mg/kg/day 50.0% of those with ≥ 100 or more mg/kg/day	[64]

Table 3 continued

Treatment	Dose regimen	Treatment duration	Follow-up period	No. of patients [controls]	Age (years)	Main findings	References
(I) AMA	(I) 10–15 mg/kg	1 month–1 year	every 2–3 months	14	3–21	All three drugs relatively effective IP 4× more effective > AMA IP 2x more effective > IFN-α	[65]
(II) IFN-α	(II) 3–6 × 10⁶ U			15			
(III) IP	(III) 100 mg/kg/day			16			

$q2h$ every two hours, $q4h$ every four hours, $q6h$ every six hours, qw once per week, *SSPE* Subacute sclerosing panencephalitis, *tab* tablets, *tiw* 3 times per week, *3TC* lamivudine, *AMA* amantadine, *bid* twice daily, *biw* twice per week, *dd* divided doses, *F* female, *HC* historical controls, *IFN* Interferon, *IP* inosine pranobex, *M* male, *na* not available, *NDI* Neurological disability index

[a] Time from onset of SSPE and treatment: 4–32 months

[b] Recombinant

[c] Treated with IP or symptomatic treatment, no IFN

[d] 50.6% and 25.8% of patients were concomitantly treated by IFN and AMA, respectively

[e] Age at onset of SSPE

administration of relevant drugs should be continued even after apparent remission [65].

Human Papilloma Virus Infections

In early studies, comparing the efficacy of IP to conventional treatments (podophyllin, cryotherapy, electrocautery, CO_2 laser and surgery), a combined use of oral IP plus conventional non-surgical treatment of genital warts was found to produce more increased cure rates that conventional treatment alone [70, 71]. The authors concluded that the advantage of oral or topical treatment over hospitalisation and anaesthesia make IP a valid therapy. However, these studies had certain limitations, such as lack of placebo controls. In a multicentre, prospective, randomised, placebo-controlled study by Davidson-Parker et al. [72] it was suggested that IP may be worth considering as adjunct to conventional treatment (primary podophyllin or trichloroacetic acid) of patients with refractory genital warts.

A randomized, double-blind, placebo-controlled study demonstrated a significant pharmacological activity of oral IP in subclinical HPV infection of the vulva [73]. Moreover, involvement of HPV in chronic vulvodynia is suspected, based on identifications of acetowhite vulval lesions. Although limited data exists on this topic, it was suggested that oral IP could also serve as a non-invasive alternative for the treatment of young women with chronic vulvodynia [74].

The efficiency and toxicity of IP has been investigated in the combined treatment of patients infected with HPV 16 and 18, manifesting epithelial dysplasia and preinvasive cancer of the cervix uteri [75]. Following a course of IP treatment, HPV 16 and 18 were undetectable in 77.8% and 50% of treated patients, respectively. A second or third course of treatment was required for only a small proportion of patients.

Of the 17 treated individuals registered in a randomised, placebo-controlled study on the efficacy and safety of IP in the treatment of cervical condylomata acuminata, four responded to the treatment completely, seven

responded partially and six did not respond at all. The therapeutic difference between treated women and placebo group was statistically significant. No recurrences were observed during the 12-month follow up in the complete responders. Adverse effects were mild and resolved upon completion of therapy [76].

An open trial compared the results of combined therapy using surgery and IP in a group of 25 patients with oral HPV-positive proliferative verrucous leucoplakia (PVL) against a group of 25 patients that underwent only surgery. Six months postoperatively there was a significant difference, with 18 recurrences in the patients treated by surgery alone compared to only two recurrences in those treated also with IP. Eighteen months postoperatively there were no further recurrences in the patients treated by surgery alone but two new recurrences in those treated with IP. Overall, by 18 months follow-up, there were 18 recurrences in the surgery-treated group, and only four in the IP group. The use of this antiviral agent appeared to offer a significant enhancement to the surgical management of PVL [77].

Studies of the effect of IP in patients with HPV infections are summarised in Table 4. Considerable efficacy with insignificant and reversible adverse effects and with low rate of recurrences is supported, hence IP may represent an efficacious and safe alternative therapy for HPV infections.

Influenza and Rhinovirus Infections

While treatment with IP in a total daily dose of 6 g had no statistically significant effect on the clinical course and serology of experimental infection due to rhinovirus 44 or rhinovirus 32 [78], a total daily dose of 4 g effected a significantly lower incidence and severity of rhinovirus 21 infection (vs. placebo) [79].

A study in volunteers challenged intranasally with influenza virus has shown significantly reduced symptomatology for the treated group [80]. Additively to them, the efficacy and safety of IP have been supported in a recent Phase 4 randomized, placebo-controlled, double-blind study [81] in subjects with clinically diagnosed

influenza-like illness, including subjects with laboratory-confirmed acute respiratory viral infections due to influenza A or B virus, RSV, adenovirus, or parainfluenza virus 1 or 3 [81]. The study results indicate the safety of IP for the treatment of subjects with laboratory-confirmed acute respiratory viral infections and confirm the efficacy of IP versus placebo in healthy non-obese subjects less than 50 years of age with clinically diagnosed influenza-like illnesses [81]. Statistically significant differences in time to resolution of influenza-like symptoms were obtained for the IP subgroups containing subjects less than 50 years of age who were without related ongoing disease and subjects of less than 50 years of age who were non-obese.

Type B and C Viral Hepatitis

IP was considered ineffective for patients in the acute phase of classical acute viral hepatitis [82]. In a double-blind, placebo-controlled study, 30 patients with HBsAg-positive acute hepatitis were administered 6 g/day of IP for a mean duration of 28 days [83]. Treatment and placebo groups were comparable as to clinical symptoms and signs, and hematological and immunological parameters. After 4 weeks of therapy, the IP group had significantly less asthenia, anorexia and splenomegaly, lower total bilirubin, transferases and alkaline phosphatase concentrations, and greater well-being. There was no statistically significant difference in abdominal malaise, nausea or hepatomegaly. Within 90 days from therapy initiation, a significantly greater number of treated patients were HBsAg-negative.

Immunomodulation therapy for patients with hepatitis C virus infection has been addressed only in individual cases or small groups of people [84, 85]. Use of IP, as monotherapy or in combination with ribavirin, had no impact on viral load. Similarly, the increase in levels of alanine aminotransferase were not considered important. However, normalization of alanine aminotransferase levels was observed in patients non-responsive to IFN treatment [85]. In addition, concomitant use of IP with ribavirin improved disease severity and

Table 4 Summary of studies on the efficacy of IP administration in patients with HPV infections

Infected loci	Treatment	Dose	Duration of treatment	No. of patients [controls]	Age (years)	Comments	References
Genital warts	IP cream	20% topical cream applied four times daily	8–9 days	5 (1 F, 4 M)	19–32	3 patients healed. 2 were treated with diathermic coagulation. No recurrence	[132]
	IP PO	6 tab × 500 mg/day (3 g/day)	5 day/month in, 3–6 months	31	16–58	Complete cure after 3 months: 77%. Best results for 3 g/day, 5 days/week for 3 months	[133]
Cervix, vulva/vagina	(I) CO_2 laser (II) CO_2 laser + IP PO	IP: 6 tab × 500 mg/day	5 days/month, 3 months	38 cervix + 24 vulva/vagina; 29 cervix + 35 vulva/vagina	na	Success after initial treatment: Group I: 68.4% (cervical), 33.7% (vulvovaginal), Group II: 93.1% (cervical), 94.3% (vulvovaginal). Failure after 3 months: Group I: 94.7% (cervical), 66.7% (vulvovaginal), Group II: 100% (cervical), 100% (vulvovaginal) recurring condylomata significantly reduced in Group II	[71]
F: vulva, perianal, vagina, cervix; M: glans, shaft, coronal sulcus	(I) IP PO (II) Podophyllin (+cryotherapy or electrocautery) (III) (I) + (II)	Podophyllin: tiw IP: 1 g tid	4 weeks	36 (19 F, 17 M); 91 (43 F, 48 M); 38 (18 F, 20 M)	21.2 (average)	Rate of cure: 39% (Group I), 41% (Group II), 95% (Group III). IP was more effective in patients with warts present for a significantly longer time	[70]
	IP PO vs. podophyllin or trichloroacetic	3 g/day	4 weeks	24 (10 F, 14 M) [27]	25.8	In patients with long history of genital warts: significantly improved efficacy of conventional treatment (podophyllin/trichloroacetic acid)	[72]

Table 4 continued

Infected loci	Treatment	Dose	Duration of treatment	No. of patients [controls]	Age (years)	Comments	References
Vulva	IP	1 g tid	6 weeks	22 [24]	38.3 ± 8.6	Treated vs.. control: significant vulval epithelial morphological improvement Significant improvement in the severity of pruritus vulvae	[73]
Vulva	IP	1 g tid	12 weeks	10	na	40% of patients became asymptomatic and 20% showed marked reduction Beneficial effect maintained after cessation of treatment	[74]
Cervix	IP	1 g, tid	10 days	45	32.2 ± 2.7	Following a course of IP treatment: HPV 16 and 18 were undetectable in 77.8% and 50% of treated patients, respectively	[75]
Cervix	IP PO	50 mg/kg/day	12 weeks	17 [19]	20–43	Four responded to the treatment completely, seven partially and six did not respond No recurrence during the 12 m follow-up in complete responders	[76]
Cervix	IP	2 tab, tid	14 months	28 (23 F + 5 M)	na	64% of patients completely cured without further need for treatment Significant reduction of recurrence probability	[134]

Table 4 continued

Infected loci	Treatment	Dose	Duration of treatment	No. of patients [controls]	Age (years)	Comments	References
Anogenital warts	IP	3 g/day (2 tabs, tid)	14–28 days or 5 days/week, 1–2 weeks/month, 3 months	na	20–30	IP as an adjunct to topical therapy or surgery: effectiveness of therapy: 41–87.5% Wart recurrence rate: 7–28%	[135]
Leukoplakia	(I) Surgery (II) IP + surgery	3 g, 6dd, → 1 g, bid,	3 days 2 months	25 (15 F, 10 M) [25]	30–69	By 18 months follow-up: 18 recurrences in Group I vs. four in Group II	[77]
Flat warts (Verruca plana)	IP cream	20% cream, qid	9–12 days	4	11–21	Three cases were resolved	[132]
Common warts (Verruca vulgaris)	IP cream	20% cream, qid	8–12 days	6	19–50	Recurrences in all patients; diathermic coagulation was eventually applied	[132]

bid twice a day, *d* divided doses, *F* female, *IP* inosine pranobex, *M* male, *na* not available, *PO* oral qid; 4 times/d, *tab* tablets, *tid* thrice/d, *tiw* twice per week

liver inflammation, evidenced by a reduction in the levels of the IFN-γ-inducible protein 10 [84]. If similar results are obtained in the future in controlled studies with larger numbers of patients, the beneficial role of IP, especially in the case of patients non-responsive to mainstay treatments, could be established.

Persistent Generalised Lymphadenopathy, HIV, and Acquired Immunodeficiency Syndrome

Evidence from early studies suggested that IP may improve some of the clinical symptoms associated with PGL in immunosuppressed males. In a placebo-controlled study in immunologically suppressed homosexual males with PGL, a total oral daily dosage of 3 g IP administered for 28 days also appeared to stimulate positive clinical effects [18, 86]. A greater percentage of drug-treated than placebo patients had an improvement in qualitatively assessed clinical symptoms, i.e., well-being, increased appetite, weight gain, night sweats, fever, skin rashes and lymph node pain.

The efficacy and safety of IP in patients infected with HIV and with no manifestation of AIDS was investigated within a placebo-controlled study, including a total of 831 male and female patients. Use of IP was found to be safe, as no serious side effects were reported. In addition, an effective delay in the progression to AIDS has been observed in the treated group [87]. Kovacs et al. [88] investigated the mechanism through which IP prevents *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia in patients infected with HIV, thus decreasing progression to AIDS. The plausible explanation provided was inhibition of the metabolism of *P. jiroveci*, in particular of dihydropteroate synthetase by p-acetamidobenzoic acid, one of IP's components [88].

Besides the positive results emerging from these studies, showing that IP can both improve clinical symptoms and delay progression of HIV infection, it has also been described that its concomitant administration with zidovudine may have advantageous effects in HIV-infected patients [89].

Autoimmune Diseases

Positive immunomodulating effects of IP have been demonstrated in several studies on patients with autoimmune diseases, such as alopecia, rheumatoid arthritis or aphthous stomatitis, but further investigation is warranted to determine the efficacy of IP in the treatment of specific autoimmune diseases. In therapeutic studies, positive clinical effects of IP, at doses of 25–50 mg/kg daily (1.5–3 g), have been reported in the majority of treated patients with aphthous stomatitis [41] and alopecia [39, 40, 90].

In a randomized, placebo-controlled, double-blind study in patients with rheumatoid arthritis, a daily dose of 3 g IP failed to produce any positive therapeutic results [4]. Notably, the same treatment regimen has been found to be beneficial in terms of morning stiffness, tender joints, proximal interphalangeal joint circumference, sedimentation rate and fibrinogen level [91–93]. Consequently, use of IP as a second-line activity in rheumatoid arthritis would need more supportive evidence.

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is characterised by symptoms such as severe fatigue, exercise intolerance, myalgia, cognitive deficit, dizziness and problems in sleep, thinking and concentration. It is most common in people between 40 and 60 years old, but it can also affect children, adolescents, and adults of all ages, with women being more susceptible. Its pathogenicity has not been yet defined, and it remains undiagnosed in approximately 90% of affected people. It is speculated that changes in the immune system, such as chronic production of cytokines, decreased NK activity and differences in markers of T-cell activation, may contribute to the onset of CFS. There is no cure or established treatment for CFS, and healthcare professionals are mainly trying to cure the symptoms rather the disease itself [94].

The safety and efficacy of IP in CFS were investigated in a single-blind, placebo-controlled study of 16 CFS patients, with a mean

age of 45.6 years [17]. Ten patients were randomly assigned to a regimen of IP for 12 weeks, consisting of 3 g/day on the odd weeks and 1 g/day on the even weeks, and six patients received methylcellulose placebo tablets. Following the 12 weeks of treatment, patients from both the treatment and the placebo groups received IP for 16 more weeks. Immune measures as well as responses of the patients to three tests, i.e., the Activities of Daily Living Questionnaire, the Cognitive Deficit Subset of the Symptom Checklist Questionnaire and the Karnofsky Performance Score, were evaluated.

Of the ten patients treated initially with IP, six reported improvement in their symptoms (improved group) and the median percentage reduction in cognitive symptoms for this group was 16%. The results from this study suggest that patients with CFS could benefit from treatment with IP. Nevertheless, further studies are warranted, with an adequate sample size and a longer follow-up period, in order to extract firm conclusions as to the efficacy of IP.

Multiple Sclerosis

Multiple sclerosis (MS) is one of the most common neurological disorders and causes of disability in young adults. Most people with MS have a normal or near-normal life expectancy. It may happen that some people with MS will experience little disability during their lifetime; nonetheless, up to 60% are no longer fully ambulatory 20 years after onset, with major implications for their quality of life. In rare cases, MS can be terminal. Globally, the median estimated prevalence of MS is 30 per 100,000, with the greatest prevalence in Europe (80 per 100,000), followed by the Eastern Mediterranean (14.9), the Americas (8.3), the Western Pacific (5), South-East Asia (2.8) and Africa (0.3). MS is more frequent in high-income countries (89 per 100,000). The global median estimated incidence of MS is 2.5 per 100 000 per year, with Europe ranking first (3.8 per 100,000), followed by the Eastern Mediterranean (2), the Americas (1.5), and the Western Pacific [95].

Use of IP in the treatment of MS has been investigated in several studies (see Hommes and Comi [96] and references therein). Significant beneficial changes were observed in patients with relapsing–remitting MS treated with IP, in regard to the mean annual relapse rate, the Kurtzke Disability Status Scale values, and the mean period of standard corticosteroid therapy [97]. In contrast to that, no significant difference in the clinical course of the disease between IP-treated patients and the control group were observed in 11 patients over a treatment period of 60 days [98].

The immunological and clinical beneficial effects of IP therapy in patients with exacerbating remitting MS were supported in the study by Pompidou et al. [99]; however, no firm conclusions could be drawn as to the long-term effectiveness of IP. A total of 52 patients with relapsing–remitting and relapsing–progressing MS were included in a double-blind, randomized, and placebo-controlled study, during which they were administered 3 g of IP or placebo for 2 years following a single, pulsed, intravenous administration of methylprednisolone. No benefit was demonstrated in the relapse rate, yet the expanded disability status scale and ambulation index show increased favor for the IP group, especially in the relapsing–remitting MS patients [100].

It is evident that outcomes from different studies are conflicting. Methodological bias makes it difficult to evaluate a potential benefit. There were major differences between the dosages, treatment regimens, patient selection and number, follow-up, and errors in randomization of patients in the treated and placebo groups.

Other Diseases and Infections

Worldwide, tuberculosis (TB) is one of the top ten causes of death, and it strikingly ranks above HIV/AIDS. The global incidence of TB for 2017 was approximately 10 million. Prevalence is higher in male adults. In 2017, the proportion of people who died from TB was 16%. Among HIV-negative and HIV-positive people, TB is estimated to have caused 1.3 and 0.3 million deaths, respectively. About 23% of the world's population is estimated to have a latent TB

infection [101] which, together with the length of treatment, malnutrition and weak immunity, are the major obstacles in controlling the TB epidemic [102]. The bacille Calmette–Guérin vaccine has been shown to prevent severe forms of TB in children, yet no such vaccine exists for adults, either before or after exposure to TB infection. The currently recommended treatment for cases of drug-susceptible TB is a 6-month regimen of four first-line drugs, i.e., isoniazid, rifampicin, ethambutol and pyrazinamide. However, drug-resistant TB continues to be a public health crisis. Approximately 600,000 people worldwide in 2017 developed TB resistant to rifampicin, the most effective first-line drug, and, of these, 82% had multidrug-resistant TB [101].

The efficacy of IP against *Mycobacterium tuberculosis* has not so far been tested. IP enhances TNF-α and IFN-γ (Th1 cytokines), stimulates T-lymphocyte differentiation into T-cytotoxic cells and T-helper cells and potentiates lymphoproliferation, both in vitro and in vivo. This resembles crucial responses of the host immune system during early stages of *M. tuberculosis* infection used to evade the pathogen. Based on this, Mishra et al. [103] suggested that the use of IP as an adjunct anti-tuberculosis chemotherapy should be considered, as potentiation of innate immunity by IP in combination with the direct inhibitory activity of the anti-TB drugs could help fight the infection while at the same time allowing for the reduction of drug doses and side effects [103]. Mishra et al. [103] have also outlined a strategy for evaluating repurposed IP for the treatment of tuberculosis.

Conclusions from a randomized, double-blind study on 22 children, aged 2.7–16.8 years with early dengue infection, suggest that IP could be used along with standard approved fluid and anti-pyretic therapy [104].

In vivo studies of the effect of IP on *Echinococcus multilocularis* and *E. granulosus* metacestodes (Cestoda), the causal agents of hydatid disease, have been performed, using jirds and mice as experimental hosts. Short- and long-term treatments with different doses (ranging from 0.5 to 4 g/kg) were tested. Marked ultrastructural damage with metabolic perturbations was observed in a dose-dependent mode

[105, 106]. Evidence for direct interaction of IP with *Echinococcus* has been provided by Lawton et al. [107].

CONCLUSIONS

Inosine pranobex is a synthetic agent with immunomodulating and antiviral properties currently indicated for the treatment of various viral diseases, among which SSPE, HSV, and varicella infections, respiratory infections, influenza, and viral hepatitis, and as an adjuvant therapy for HPV infections.

In almost 50 years since its initial authorization, IP has been assessed extensively in herpes simplex genitalis and labialis and encouraging clinical results have been reported. The drug has been found to be clinically useful in SSPE, either as a monotherapy or as part of a combination regimen, usually with IFN-α. In the treatment of genital warts, the combined use of oral IP and conventional non-surgical treatment has resulted in greatly increased cure rates versus the rates for conventional treatment alone. Individual double-blind, placebo-controlled studies in immunologically depressed homosexual men with persistent generalized lymphadenopathy treated with IP also had a positive outcome. Statistically significant clinical benefits of the use of IP have been reported for patients with type B viral hepatitis. The efficacy and safety of IP have also been supported in patients with influenza and influenza like illnesses.

In various cases, the positive effects from the administration of IP, either in animal models or humans, have been time-limited or there was a recurrence of symptoms. Consequently, treatment with IP should be repeated and be long-term, especially in some chronic infections [36, 42, 53, 108].

In recent years, the increased understanding of the antiviral immune mechanisms, the limited number of approved drugs for medical use against HSV and the occurrence of drug-resistant HSV strains have encouraged even more the administration of IP as part of a combination therapy for HSV patients, especially those infected with viral strains resistant to currently

known antiviral drugs. Likewise, synergistic use of IP together with other agents, such as IFN-β and lamivudine, can help achieve enhanced clinical responses and survival rates of SSPE patients, but further investigation is warranted. Recently, limited data indicate that the use of IP may be extended to other HPV-related diseases (e.g., leukoplakia, cervix dysplasia, etc.). Emerging data concerning diseases for which no treatment exists and IP has been found or speculated to have positive effects (e.g., chronic fatigue syndrome, multiple sclerosis, tuberculosis, etc.), should attract more attention and be further investigated. Although TB is curable, treatment protocols are complex and lengthy, hence difficult to adhere to. The emergence of multidrug-resistant *M. tuberculosis* strains and the association of TB with HIV have further exacerbated the problem [102]. In this regard, the repurposing and revival of existing drugs, such as IP, which are currently in use for other diseases could be an excellent strategy to meet the urgent requirement of new drugs [103].

The use of a drug with a safety profile such as that of IP in fatal and/or debilitating diseases, such as SSPE or AIDS, or even in painful, recurring and/or psychologically traumatic diseases, such as herpes and HPV infections, is greatly needed and tempting but challenging at the same time. To fully support the value of IP, placebo-controlled, dose–response studies, well-designed and reported in terms of, e.g., target populations, treatment duration, and efficacy markers are warranted. Additional efforts to investigate the direct antiviral activity of IP and correlate it with the clinical outcome following treatment would help to further elucidate the mechanism of action of IP. In such a manner, the safety and quality of life of patients will be better served, the place of the drug in therapy of various diseases will be firmly established, and possibly new indications for IP will be unveiled.

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