The Use of Interferons in the Treatment of Cutaneous T-Cell Lymphoma

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KEYWORDS

• Cutaneous T-cell lymphoma • Interferons • Interferon alfa • Interferon gamma • Mycosis fungoides • Sézary syndrome

KEY POINTS

- Interferons (IFNs) have various immunomodulatory functions that are likely conducive to the treatment of cutaneous T-cell lymphoma (CTCL).
- IFN alfa and IFN gamma are the 2 types of IFNs that have primarily been used in the treatment of CTCL.
- IFNs can cause various laboratory abnormalities and side effects that do not typically necessitate cessation of therapy, but do require close monitoring on the part of the prescribing physician.
- Although there is a problematic lack of randomized controlled trials assessing the use of IFNs in CTCL, many studies have argued their efficacy in patients with various stages of CTCL.

INTRODUCTION

IFNs are polypeptides produced by stimulated eukaryotic cells and naturally occur in the human body as a part of the innate immune response.[1] Although IFNs were originally named in 1957 as a result of their ability to interfere with viral replication,[2] they have since been shown to also have cytostatic and immunomodulating functions.[3] Recognizing the potential for such functions to combat disease, researchers have used recombinant DNA technology to produce 3 major types of IFNs, which are commercially available products approved by the US Food and Drug Administration (FDA) in the United States. These products include IFN alfa, IFN beta, and IFN gamma. Although subsequent sections of this article focus almost entirely on the properties of the IFNs most commonly used in patients with CTCL, it first examines some of the basic attributes of the naturally occurring IFN counterparts.

Viruses, B-cell mitogens, foreign cells, and tumor cells stimulate leukocytes and lymphoblastoid cells to produce IFN alfa,[4] while T-cell mitogens, interleukin (IL)-2, and other antigens stimulate T cells and natural killer (NK) cells to make IFN gamma.[5] Viruses and foreign nucleic acids stimulate fibroblasts and epithelial cells to produce IFN beta.[4] As both are stable at the acidic pH of 2 and they bind to the same IFN surface receptors, IFN alfa and IFN beta are designated as type I IFNs.[5,6] In contrast, because IFN gamma is not stable at such an acidic pH and binds to a different IFN surface receptor, it is considered a type II IFN.[3]

As alluded to above, IFNs have demonstrated antiviral, cytostatic, and immunomodulatory functions. IFN seems to exert its antiviral impact via the stimulation of enzymes, which then induce the cleavage of viral RNA, the inhibition of protein synthesis, and the production of antiviral proteins.[7]

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IFNs are cytostatic by their direct inhibition of cell cycle progression through the S phase[8] and possibly by stimulating enzymes that block protein synthesis.[9,10] The immunomodulatory functions of IFN alfa and IFN gamma therapies are discussed in detail in the Mechanism of Action sections. As literature has rarely addressed the use of therapeutic IFN beta in CTCL, the authors only discuss it briefly.

INTERFERON ALFA

Although alfa-type IFNs are primarily prescribed for the treatment of hepatitis C, the National Comprehensive Cancer Network guidelines have long included IFN alfa in its recommended treatments for the most common types of CTCL, mycosis fungoides (MF) and Sezary syndrome (SS).[11] Multiple studies have examined the use of commercially available IFN alfa in patients with all stages of MF/SS. Most studies assessing the efficacy of alfa-type IFNs in the management of MF/SS have considered 2 forms of recombinant IFN alfa, IFN alfa-2a (Roferon) and IFN alfa-2b (Intron-A), which are produced via genetically engineered *Escherichia coli*-containing DNA that codes for human protein.[10,12] Roferon is no longer manufactured in the United States. IFN alfa-2a and IFN alfa-2b share nearly identical structures because they only differ in their manners of purification and by a single amino acid[3]. These differences do not appear to impact their antigenicity as both of these IFNs seem to bind to an identical type I IFN receptor.

The pegylated forms of IFN alfa-2a and IFN alfa-2b are called Pegasys and PegIntron, respectively, and are larger in size than their nonpegylated counterparts.[14] Despite the lack of large studies or clinical trials assessing these pegylated IFNs in CTCL, the use of pegylated IFN alfa-2b for this indication has been reported, so the authors discuss it when possible. Other commercially available IFN alfa's (ie, IFN alfa-n3 and IFN alfacon-1), have not been used in the treatment of MF/SS[12,13] and are not discussed in this article.

Mechanism of Action

Although IFN alfa has cytostatic and antiviral properties like other IFNs, its immunomodulatory effects seem to be particularly conducive to combating the immune dysfunctions observed in CTCL. To provide a better foundation for understanding the properties that appear to make IFN alfa an effective therapy for MF/SS, it is helpful to first discuss the proposed mechanisms of immune dysregulation in these cancers.

The malignant T cells in MF/SS are typically mature skin-honing memory $CD4^+$ helper T cells, which exhibit a T-helper type 2 (T_H2) phenotype in their release of elevated amounts of IL-4, IL-5, and IL-10 cytokines.[15–17] This increased T_H2 activity seems to create a cytokine imbalance that suppresses the host's T_H1-mediated immune activity[18]; this is consistent with research showing that factors produced by T_H2 cells counter T_H1 activity.[19,20] Studies have argued that decreased production of IFN gamma,[15] IL-12, and IFN alfa[15,21,22] provide evidence of decreased T_H1 activity in patients with MF/SS and that some of these immune abnormalities may underlie both the decreased activity and numbers of dendritic cells (DCs) observed in MF/SS.[22] In addition to diminished T_H1 immune activity and DC numbers and activity, other proposed mechanisms of deficient immune activity in MF/SS include decreased numbers and activities of both NK cells and $CD8^+$ T cells.[23,24] These immune defects could be means by which the cancer compromises the host immune system's abilities to not only combat infection but also mount an effective antitumor response.[25] Although not necessarily a marker of immune deficiency, peripheral eosinophilia and elevated serum immunoglobulin E levels are other immune abnormalities observed in MF/SS.[15,26] In addition to portending a worse prognosis in MF/SS,[27] peripheral eosinophilia in general has been associated with adverse events.[28]

IFN alfa seems to ameliorate several of the immune defects described above. Specifically, IFN alfa appears to activate $CD8^+$ T cells and NK cells[23] and to suppress the problematic increase in T_H2 activity by inhibiting Sézary cell and normal T-cell production of IL-4 and IL-5.[29–33] IFN alfa may further augment cytotoxicity by increasing the expression of class I molecules on lymphocytes.[34] In addition, culturing the peripheral blood of patients with SS with recombinant IFN alfa was observed to significantly inhibit the excess production of IL-5, a cytokine that stimulates the proliferation of eosinophils.[31] As noted above, peripheral eosinophilia has been associated with worse prognosis and adverse events. **Fig. 1** adapted from Kim and colleagues[25] summarizes these proposed targets of IFN alfa therapy in MF/SS.

It is worth mentioning in this section that some investigators have reported the development of resistance to IFN alfa.[35,36] Downregulation of IFN receptors,[37] production of neutralizing antibodies,[10,38] and loss of STAT1 expression in the malignant T cell[39] are purported mechanisms of resistance.[40]

Pharmacokinetics

IFN alfa is typically administered as a subcutaneous (SC) injection in patients with CTCL.

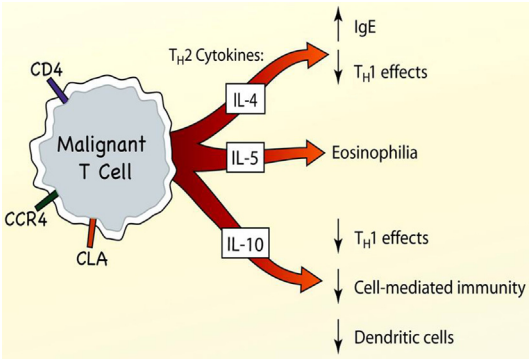

Fig. 1. Pathologic immune abnormalities in CTCL that likely serve as targets of IFN therapy. CCR4, chemokine (C-C Motif) receptor 4; CLA, cutaneous lymphocyte-associated antigen. (*Adapted from* Kim EJ, Hess S, Richardson SK, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest 2005;115(4):804; with permission.)

Nonpegylated IFN alfa administered through intramuscular (IM) or SC injections reaches peak serum concentration within 2 to 6 hours.[6] The elimination half-life of nonpegylated IFN alfa-2b is 2 to 3 hours and that of nonpegylated IFN alfa-2a is slightly longer. The pegylated forms of IFN alfa have much longer elimination half-lives than their nonpegylated counterparts. This prolonged half-life is because the addition of polyethylene glycol to their structures makes them more resistant to breakdown by proteolytic enzymes than the nonpegylated forms. The elimination half-life of pegylated IFN alfa-2a is approximately 80 hours, whereas that of pegylated IFN alfa-2b is approximately 40 hours.[3,40] In addition, pegylated IFN alpha-2b acts primarily as a prodrug with its slow IFN release.[14]

IFN alfa is metabolized by the liver, filtered through the glomeruli, and undergoes degradation during tubular resorption.[12] IFN alfa has also been administered intralesionally in MF. Although this method is safe, the systemic absorption of the IFN may be decreased.[41,42]

Typical Dosing

The following discussion focuses mostly on nonpegylated IFN alfa dosing and is gleaned from research on both IFN alfa-2a and IFN alfa-2b with the underlying assumption that because these types of IFN alfa are nearly biologically identical, they should behave almost equivalently. However, such an assumption is likely imperfect because some differences do exist between the 2 compounds.[3]

There is a wide range of doses reported in literature examining the use of IFN alfa in MF or SS. The maximally tolerated dose of nonpegylated IFN alfa has been reported to be 9 to 18 million units (MU) daily, but most clinicians seem to treat patients with 3 to 6 MU thrice weekly or daily.[35,43–45] It has been suggested that patients who are initially administered lower doses before being escalated to higher doses tolerate the higher doses better than individuals who are initially administered higher doses.[46] As discussed earlier, IFN alfa may also be administered intralesionally. If only aiming to treat the injected plaque or tumor, injecting 1 to 2 MU into the lesion 3 times a week until significant improvement is observed is reasonable.[41,42]

There is some suggestion that higher doses of IFN alfa, if tolerated, are more effective than lower doses.[35,47,48] Several patients in the study by Olsen and colleagues,[35] which randomized patients to 36 MU versus 3 MU per day, were able to achieve complete remission only after their dose was increased or the higher dose was continued for longer than the 10-week induction period.

Unlike nonpegylated IFN alfa, which is generally given as fixed doses unrelated to patient weight, pegylated IFN alfa-2b should be dosed according to the formula 1.5 μg/kg/wk. However, at the authors' center at the Hospital of the University of Pennsylvania, patients are typically initially administered approximately half of this dose and then the dose is eventually increased to 1.5 μg/kg/wk as tolerated. In contrast to the variable frequency of nonpegylated IFN alfa, pegylated IFN alfa-2b or IFN alfa-2a is given as a once-weekly injection because of its extended half-life.[49]

The lack of large-scale randomized controlled trials assessing IFN alfa in MF/SS has meant that its precise use, particularly in regard to duration of therapy, is highly institution dependent. For example, Elise Olsen of Duke University's Department of Dermatology has described her typical regimen as the following. Nonpegylated IFN alfa is usually started at 3 MU thrice weekly; half the dose is administered in elderly or debilitated patients for the first 2 weeks. Response is assessed at 3 months, and if at that time there is minimal to no response, then either the IFN is escalated to 3 MU daily or a retinoid is added. If the patient attains a complete response (CR), Olsen recommends continuing that dose for at least 3 months thereafter and then slowly reducing the dose or frequency over the following 6 to 12 months in the absence of relapse.[3] Although there is some evidence that the efficacy of IFN alfa could persist in patients who attain partial responses (PRs) on higher doses and are then administered lower doses for maintenance,[44,46] others contend that objective response (OR) could be compromised by a premature dose reduction before attaining a

CR.[35] If using pegylated IFN, because of the unavailability of multidose vials, Olsen either begins at 50 or 80 μg of pegylated alfa-2b (PegIntron) weekly taking into account the weight, age, and physical condition of the patient, escalating to 120 or 180 μg weekly, or instead uses 90 μg of pegylated IFN alfa-2a (Pegasys) weekly escalating to the higher dose vials of 135 or 180 μg weekly as tolerated—there is no preference for either pegylated forms, but one or the other may be preferred by a patient's insurance carrier.

In slight contrast to the approach described above, the authors' practice typically involves starting nonpegylated IFN alfa-2b, 1.5 MU thrice weekly, and then escalating the dose as tolerated to 3 MU thrice weekly. If the patient does not improve at such a dose after 3 months of therapy, the authors typically increase the frequency to 4 times weekly or increase the dose up to 5 MU. After 3 to 4 months without improvement on such a regimen, the authors add other therapies before altering the therapeutic approach. If using pegylated IFN alfa-2b, the authors administer 0.75 to 1.5 μg/kg/wk. However, if the patient does not show improvement after 3 to 4 months, the authors do not escalate the dose. Instead, they add an additional therapy and may either stop or continue the pegylated IFN alfa-2b.

Although a lack of clear recommendations regarding duration of therapy is frustrating, a benefit of IFN alfa therapy over many other systemic treatments for MF or SS is that it is not associated with chronic cumulative dose effects or secondary malignancies such that its long-term use seems safe in most patients.[3] However, there is a small risk of new or exacerbated autoimmune disease during long-term therapy (see sections Adverse Effects).

Response to Therapy

While there are many prospective studies and retrospective case series evaluating IFN alfa in MF/SS, there are few randomized controlled trials. Despite this, it is widely accepted that IFN alfa can be effective in all stages of MF or SS.[3] In this section, some of the largest published studies of IFN alfa in patients with MF/SS are detailed. Readers may refer to **Table 1** for a synopsis of published studies that assess IFN alfa in 20 or more subjects with MF or SS.

Interferon alfa alone

In 1984, Bunn and colleagues[13] first argued the efficacy of IFN alfa in CTCL. In this prospective trial, 20 patients with what was described as advanced-stage disease (5 with stage II, 2 with stage III, and 13 with stage IV MF using the TNM staging system) were initially given significant doses (50 MU) of IFN alfa-2a thrice weekly and with dose reduction if side effects were intolerable. Of the 20 patients, 9 patients (45%) experienced a PR with a median response duration of 5 months. No patient experienced a CR. Not surprisingly, all patients required dose reductions to at least 50% of the initial dose because of intolerance. In response to the demonstrated difficulty in tolerating such high doses of IFN alfa, a subsequent 1990 trial by Kohn and colleagues[50] attempted to use pulse doses of recombinant IFN alfa-2a. Patients were given 10 MU on day 1 followed by 50 MU on days 2 to 5 every 3 weeks. Of the 24 subjects enrolled in this trial, 1 patient had a CR and 6 subjects had PRs; this resulted in a 29% OR rate, and the median response duration was 8 months. Readers may refer to **Table 1** for study details. Since the study by Kohn and colleagues,[50] clinical trials have typically dosed IFN alfa 1 to 3 times weekly, not in a pulsed manner.

Papa and colleagues[45] prospectively analyzed 43 patients with stage I to IVB CTCL who received between 3 and 18 MU IFN alfa-2a (whatever dose each subject maximally tolerated) thrice weekly for 3 months, and responders were then continued on their maximally tolerated doses for 6 months. This study showed an impressive OR in 70% of patients with stage III or IV disease and in 80% of those at lesser stages. Among this study's subjects were 28 newly diagnosed and previously untreated patients. Not surprisingly, the study reported a greater overall response rate in the previously untreated subjects. However, the difference was not marked (79% or 22 of 28 previously untreated subjects vs 67% or 10 of 15 previously treated subjects). These findings complement those of the multicenter controlled trial by Olsen and colleagues,[35] which included patients with stage IA to IVA disease treated with IFN alfa-2a, 3 MU daily (n=8) or 36 MU daily (n=14). At the end of 10 weeks, all on the higher dose required a dose reduction, including decrease in dose in 6 of 14 patients to 3 to 3.6 MU/d; 10 patients (45.5%) had a PR (including 3 patients with stage IIB MF), 3 patients (13.6%) achieved a CR, 2 of which had stage IVA disease. An additional 3 patients achieved a CR with longer treatment times (27% overall) with a duration of CR in these 6 patients of 4 to 27.5 months. Overall response was greater in those receiving higher doses. Another prospective trial by Tura and colleagues[46] found that all 15 of its subjects (stage II–IV) experienced some reduction in skin lesions (3 CR, 9 PR, and 1 mild response) in response to IFN alfa-2a with a dosing protocol dispensing 3 to 18 MU daily for 3 months followed by 18 MU thrice

Table 1
Studies of at least 20 subjects assessing IFN alfa both alone and in combination with other treatments

Study, Year	Design	Treatment[a]	Number of Subjects, Stage Range of Subjects	Key Results
Bunn et al,[13] 1984	Prospective observational	IFN alfa-2a	20, stage II–IVB	9/20 (45%) achieved PR, 0/20 (0%) achieved CR, responses did not correlate with stage, extremely high (50 MU/wk) doses of IFN used, all subjects required dose reduction
Olsen et al,[35] 1989	Prospective observational	IFN alfa-2a	22, IA–IVA	3/22 (14%) achieved CR and 10/22 (45%) achieved PR after 10 wk, 2 patients with PR and 1 patient with stable response then went into CR with further treatment, remissions lasted 4–27.5 mo, response was greater at higher doses than at lower dose
Kohn et al,[50] 1990	Prospective observational	IFN alfa-2a	24, IA–IVB	1/24 (4%) achieved CR, 6/24 (25%) achieved PR, no improvement seen in 8 patients who received dose escalation
Papa et al,[45] 1991	Prospective observational	IFN alfa-2a	43, I–IVB	11/43 (26%) achieved CR, 21/43 (49%) achieved PR, greater response in previously untreated subjects
Stadler et al,[56] 1998	Randomized clinical trial	IFN alfa-2a with PUVA vs IFN alfa-2a with acitretin	98 randomized, 82 evaluable, stage IA–IIB	28/48 (70%) patients receiving IFN and PUVA achieved CR (26/31 stage I, 2/9 stage II), 16/42 (38%) receiving IFN and acitretin achieved CR (16/33 stage I, 0/9 stage II), median time to CR much shorter in IFN and PUVA group (18.6 wk) than IFN and acitretin group (21.8 wk)
Jumbou et al,[51] 1999	Retrospective observational	IFN alfa-2a	51, IA–IV	21/51 (41%) achieved CR (5/8 stage I, 1/1 stage IIA, 13/30 stage IIB, 2/11 stage III, 0/1 stage IV), 13/51 (25%) achieved PR (2/8 stage I, 0/1 stage IIA, 10/30 stage IIB, 1/11 stage III, 0/1 stage IV), mean time to CR was 4 mo and independent of stage
Kuzel et al,[36] 1995	Prospective observational	PUVA with IFN alfa-2a	39, IB–IVB	24/39 (62%) achieved CR, 11/39 (28%) achieved PR, median response duration was 28 mo
Chiarion-Sileni et al,[57] 2002	Prospective observational	PUVA with IFN alfa-2a	63, IA–IVA	51/63 (75%) achieved CR, 6/63 (10%) achieved PR, median response duration was 32 mo
Rupoli et al,[59] 2005	Prospective observational	PUVA with IFN alfa-2b	89, IA–IIA	75/89 (84%) of subjects achieved CR (82% of stage IA, 87% of stage IB, 73% of stage IIA), median time to CR was 6 mo
Nikolaou et al,[58] 2011	Retrospective observational	PUVA with IFN alfa-2b	22, IB–IVA	10/22 (45%) achieved CR, 5/22 (23%) achieved PR, more subjects in early stages (stage IA-IIA) achieved CR than those in later stage (IIB–IV) (96% vs 27%, *P* value .03)

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Table 1
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Study, Year	Design	Treatment[a]	Number of Subjects, Stage Range of Subjects	Key Results
Wozniak et al,[60] 2009	Randomized clinical trial	PUVA vs PUVA with IFN alfa	29, IA–IIA	13/17 (76%) subjects on PUVA alone achieved CR, 9/12 (75%) on PUVA and IFN achieved CR, none of the 29 patients achieved PR
Hüsken et al,[62] 2012	Retrospective observational	PUVA with pegylated IFN alfa-2a vs PUVA with nonpegylated alfa-2b	17, IA–IV	4/9 (44%) achieved CR and 4/9 (44%) achieved PR in PUVA with pegylated IFN alfa-2b group, 3/8 (38%) achieved CR and 1/8 (13%) achieved PR in PUVA with IFN alfa-2a group, higher rate of myelosuppression and liver toxicity and lower rate of constitutional side effects in pegylated combination group
Wagner et al,[76] 2013	Retrospective observational	TSEBT alone vs TSEBT with IFN alfa-2b	41, IA–IVA	63% of subjects on combination achieved CR and 36% of subjects on TSEBT alone achieved CR but this difference was not statistically significant, no difference in overall survival and progression-free survival detected between the 2 groups

CR is the complete clearance of all skin lesions lasting at least 4 weeks and PR is at least 50% reduction of skin lesions lasting at least 4 weeks; wk ,weeks; mos, months.
Abbreviations: PUVA, psoralen plus ultraviolet A; TSEBT, total skin electron beam therapy.
[a] IFN administered is nonpegylated unless otherwise noted.

weekly for 6 months. However, this study also found that many patients could not tolerate 18 MU daily and suggested that future trials not give subjects older than 60 years doses greater than 9 MU/day.

A larger-scale retrospective study by Jumbou and colleagues[51] looked at 51 subjects with stage IA to IV CTCL who used IFN alfa-2a monotherapy at a mean dose of 2.7 MU daily for a mean duration of 15.8 months. The investigators reported 21 subjects with CRs, 13 with PRs, and 17 with stable or progressive disease. Although CRs were more common in lower stages, time to CR and the duration for which the CR was sustained were actually independent of stage. CRs were obtained within 6 months and lasted an average of 31 months. Readers may refer to **Table 1** for further study details.

There are numerous smaller-scale studies assessing the use of IFN alfa monotherapy in CTCL. Although Estrach and colleagues,[52] Dallot and colleagues,[53] and Vonderheid and colleagues[41] demonstrated good responses to IFN alfa-2b among patients with MF/SS, the positive results in Vonderheid and colleagues'[41] study were limited to the improvement of specific plaques with intralesional injections because the study patients did not seem to improve with subsequent IM injections of IFN alfa-2b. Other small-scale studies have reported responses in patients with MF/SS of all stages to IFN alfa-2a monotherapy.[43,44,54]

Interferon alfa in combination with psoralen plus ultraviolet light phototherapy

Several studies have examined the use of concomitant IFN alfa and psoralen plus ultraviolet A (PUVA) phototherapy. Kuzel and colleagues[36] and Stadler and Otte[55] argued in their 1995 trials of 39 and 16 subjects, respectively, that the CR rates they demonstrated with the combination of IFN alfa-2a and PUVA were superior to those demonstrated in previous studies with IFN or PUVA alone. While neither study compared the combination treatment groups directly to monotherapy groups, a later prospective randomized study of 98 subjects with stage IA to IIB disease by Stadler and colleagues[56] compared the efficacy of IFN alfa-2a (9 MU thrice weekly) and PUVA (5 times weekly during first 4 weeks, 3 times weekly during weeks 5 through 23, 2 times weekly during weeks 24 through 48) with that of IFN alfa-2a (9 MU thrice weekly) and acitretin (25 mg daily during week 1, 50 mg during weeks 2 through 48). The combination of PUVA and IFN resulted in CR in 70% of subjects, whereas only 38.1% of subjects in the IFN and acitretin group experienced CR. **Table 1** provides further study details. A later study by Chiarion-Sileni and colleagues[57] found an impressive CR rate of 75% (mean response duration of 37 months) in 63 patients with stage IA to IVA disease treated with PUVA and IFN alfa-2a, but did not directly compare these results with those of subjects undergoing monotherapy. However, CRs were obtained in all stages of disease. Like Chiarion-Sileni and colleagues,[57] a case series by Nikolaou and colleagues[58] showed an impressive overall response rate of 68%. In a phase 2 prospective trial of 89 patients with stage IA to IIA CTCL by Rupoli and colleagues[59] reported an impressive overall response rate of 98% for IFN (6–18 MU weekly) and PUVA but it did not compare these results to those of patients treated with monotherapy. **Table 1** provides details of the studies by Chiarion-Sileni and colleagues,[57] Nikolaou and colleagues[58] and Rupoli and colleagues.[59]

In contrast to the results of Rupoli and colleagues'[59] study, Wozniak and colleagues[60] did not demonstrate significant differences in response to PUVA alone versus PUVA and IFN alfa in their randomized controlled trial of 29 patients with similar low-stage disease (IA–IIA). Humme and colleagues[61] conducted an overall assessment of the many trials looking at the combination of IFN alfa and PUVA including that by Wozniak and colleagues.[60] This review pooled the results of 11 selected trials that investigated the combination of PUVA and IFN alfa, including 3 randomized controlled trials, 3 prospective cohort studies, 2 retrospective case series, 2 undefined trials, and a study that included data from a retrospective analysis as well as a prospective randomized trial. Although this review calculated a mean overall response rate of 79% $\pm$ 15% across all trials, it concluded that the addition of IFN alfa did not increase the efficacy of PUVA in patch- or plaque-stage MF. The study did not address whether the time to response was decreased or unchanged with the addition of IFN to PUVA.

Although there is little mention of the use of pegylated IFN alfa in CTCL, a retrospective cohort study by Hüsken and colleagues[62] compared 9 patients with stages IA to IV CTCL (2 stage IA, 3 stage IB, 2 stage IIA/B, 1 stage III, 1 stage IV) treated with PUVA and pegylated IFN alfa-2b (1.5 μg/kg weekly) to 8 patients (2 stage IA, 4 stage IB, 1 stage IIA/B, and 1 stage III) treated with PUVA and nonpegylated IFN alfa-2a (9 MU thrice weekly). While this study concluded that myelosuppression and liver toxicity occurred more frequently in the pegylated group, it also found that overall response was much higher in the pegylated group than in the nonpegylated group (89% vs 50%). However, like many of the studies described above, its conclusions are limited by its small size.

Interferon alfa in combination with oral retinoids

Several small studies have suggested that oral retinoids and IFN alfa are more effective together than as monotherapy in the treatment of MF/SS. Straus and colleagues[63] conducted a prospective trial in which 22 patients with stage IB to IV disease were first treated with oral bexarotene (300 mg/m^2/d for 8 weeks), and then those who had not improved on bexarotene alone were given IFN alfa-2b (3–5 MU thrice weekly) in addition to bexarotene. Of the 8 of 22 subjects who had not responded to bexarotene alone and were given IFN alfa-2b, there was a 38% overall response rate (3/8) after the IFN alfa-2b was added. Other literature has suggested that combinations of IFN alfa-2b with bexarotene,[64] isotretinoin,[65] or etretinate[44,66] are effective, but such studies are limited by their small size and their failure to directly compare their results to those of monotherapy.

Interferon alfa in combination with extracorporeal photopheresis

Multiple small-scale studies have attempted to determine the efficacy of IFN alfa and extracorporeal photopheresis (ECP). One of the larger analyses was by Dippel and colleagues[67] who retrospectively compared the responses of 9 patients who received both ECP and IFN alfa-2a (3–18 MU thrice weekly) with those of 10 patients who received ECP alone and found a better response rate in the subjects on combination therapy. A prospective controlled study by Wollina and colleagues[68] assessed the use of twice-monthly ECP and IFN alfa-2a (6–18 MU thrice weekly) in 14 patients with stage IIA and IIB CTCL. After 6 months, 60% patients with stage IIA and 25% patients with stage IIB CTCL had some response (either CR or PR) to therapy. Although other case reports also promote the efficacy of IFN alfa in combination with ECP,[69–71] a pilot study by Vonderheid and colleagues[72] of 6 patients with SS did not find a significant response to treatment with ECP and IFN alfa-2b. Similarly, the only prospective study in patients with various stages of MF/SS comparing IFN alfa alone to the combination of IFN alfa and ECP failed to show an improved response of the combination regimen over IFN alone.[10] This finding is echoed by Humme and colleagues[61] who compared the findings of Wollina and colleagues[68] with those of trials assessing IFN alfa monotherapy and concluded that the combination of IFN alfa and ECP are not superior to IFN alone. This observation has raised the question as articulated by Zackheim and colleagues[73] of whether there is genuinely an additive or synergistic effect with the combination of ECP and IFN alfa and underscores the necessity of a prospective randomized clinical trial to address this.[40] Nevertheless, at the authors' center, patients with SS are routinely treated with IFN alfa and ECP, and this approach is found to be effective.[74]

Interferon alfa in combination with total skin electron beam therapy

Although there are many published examples of total skin electron beam therapy (TSEBT) being used in conjunction with IFN therapy,[74] the evidence supporting the notion that the combination of the 2 therapies is more effective than either treatment alone is lacking. A study by Roberge and colleagues[75] compared the outcomes of 31 patients with various stages of MF treated with TSEBT alone with those of 19 patients with various stages of MF treated with both TSEBT and IFN alfa. In those 19 subjects, IFN was given both concurrently with TSEBT and after the completion of the entire course of TSEBT. This study concluded that there was not a significant difference in CR, disease-free survival, or overall survival between the 2 groups (median follow-up for living patients was 70 months). Similarly, a later retrospective study by Wagner and colleagues[76] assessed 41 patients who received TSEBT either alone or in combination with IFN alfa-2b and found CRs in 63% of patients receiving the combination regimen versus in 35% of patients receiving TSEBT alone. However, this difference was not statistically significant and the study did not show a statistically significant difference in overall survival or progression-free survival between the combination and monotherapy groups. Despite such a lack of published evidence, the authors' center feels justified in concomitantly treating patients with both TSEBT and IFN given the ability of electron beam radiation to induce apoptosis in malignant T cells[77] and the probable ability of IFNs to enhance the immune system's processing of apoptosed cells.

Interferon alfa in combination with chemotherapeutics

The use of IFN alfa in conjunction with chemotherapeutics is not common. Studies by Foss and colleagues[78,79] showed an objective response in only 41% of patients with stage I to IVB MF/SS treated with pentostatin (4 mg/m^2 on days 1 through 3 every 42 days) and IFN alfa-2a (10 MU/m^2 on day 22 and 50 MU/m^2 on days 23 through 26) and in 51% of patients with stage I to IVB MF/SS treated with fludarabine (25/m^2 on days 1 through 5 every 28 days) and IFN alfa-2a (5–7.5 MU/m^2 SC thrice weekly). In marked contrast, the study by Avilés and colleagues[80] reported an impressive CR in 74% of 158 patients with stage IIB to IVA CTCL

treated with methotrexate (MTX, 10 mg/m^2 biweekly) and IFN alfa-2b (9 MU thrice weekly). The investigators did not provide a mean duration of response, but the 10-year estimated survival was 69%. It seems that a possible mechanism for this efficacy could be that MTX and IFN together enhance the expression of Fas (CD95), which augments Fas/Fas ligand-induced apoptosis of the malignant T-cell population.[81] However, the shortage of reported adverse effects in Aviles and colleagues study was unusual considering the toxicities usually associated with both MTX and IFN alfa monotherapy.[40]

Interferon alfa as part of multimodality treatment

It is perhaps most difficult to assess the efficacy of IFN alfa as part of multimodality treatment, which the authors define as 3 or more systemic CTCL agents given concurrently. In addition to IFN alfa, agents most often included in multimodality treatment include PUVA, oral retinoids, and ECP. Although there are reports of successful responses to the combinations of vorinostat/IFN alfa-2a/ECP,[82] IFN alfa-2a/ECP/PUVA,[83] and IFN alfa/ECP/IL-2[84] and retrospective cohort analyses that promote the multimodality approach,[75,85] none of the available literature includes trials that directly compare multimodality regimens to either each other or to regimens consisting of 1 to 2 treatments. Nevertheless, the authors' center routinely treats more advanced stages of CTCL with multimodality regimens that most often include IFN, an oral retinoid, skin-directed therapy, and/or ECP.

Adverse Effects

The most common acute side effects of IFN alfa are described as flulike and include fever, fatigue, chills, myalgias, arthralgias, and headache. Patients most frequently experience these symptoms during the hours immediately after the IFN injection and usually only during the first 2 weeks of treatment. Taking acetaminophen before the IFN injection can mitigate these discomforts. The most common chronic side effects of IFN alfa include fatigue, appetite loss, and weight loss (usually 2.3–4.5 kg).[3] These common side effects generally are dose related, decline in severity over time, and do not usually require dose reduction or cessation of therapy. Dose-related cytopenias (most commonly anemia, thrombocytopenia, and leukopenia) are relatively frequent side effects that may require dose reduction or stoppage of therapy if severe.[40] However, in the absence of prior chemotherapy or known primary immunosuppressive disorder, the authors' center usually does not alter dose when neutrophil counts are above 500 per mm.

While other possible side effects of IFN alfa are less common than those mentioned above, they are nonetheless worth discussing because they can become dangerous if they go unrecognized and may require dose reduction or cessation of therapy. Depressed mood and increased irritability have been reported with IFN alfa, and physicians should proceed with caution particularly in patients with a history of mood disorders. Impaired cognitive function is also possible and is usually more marked in the elderly. Thyroid dysfunction (most often hypothyroidism, but thyroiditis has been noted as well) can occur in up to 20% of patients using IFN alfa. Prescribing physicians should have a low threshold to draw thyroid function blood tests in patients with worsening fatigue despite being on a stable IFN dose. Altered taste, diarrhea, and elevated values of liver function tests may also occur but are usually mild and do not typically require dose modification. Peripheral neuropathy has been reported and, if severe, may require dose reduction or stoppage of therapy. Visual and auditory impairments, including the development of retinal cotton wool spots, are rare side effects, but such patients should immediately be referred to the appropriate specializing physicians to best assess the cause of the visual or auditory dysfunction. If IFN is deemed the likely culprit of visual or auditory impairment, the drug is usually stopped.[40]

There have also been reported cases of IFN alfa both inducing and worsening autoimmune disorders.[86] As a result, prescribers may be hesitant to use IFN alfa in patients with known autoimmune disease. In addition, IFN alfa is thought to possibly have antiangiogenic properties[87] such that the authors' center routinely stops IFN for 1 week before scheduled surgery and does not restart IFN until 1 week after surgery. Since IFN alfa was first introduced, various forms of cardiac toxicity have been reported and have included cardiac arrhythmias, cardiomyopathy, myocarditis, and myocardial infarction. However, some research has argued against the association of IFN alfa with these cardiac toxicities.[88] In addition, it seems that these events occurred at higher doses of IFN alfa than those generally used in the treatment of MF or SS. Nonetheless, patients with a history of coronary artery disease should be carefully monitored while on IFN.[40]

Although the list of possible side effects of IFN alfa is long, the vast majority of these adverse events seem reversible once IFN alfa is stopped. That there seem to be no long-range cumulative dose effects in most patients likely makes the drug safe for long-term use if tolerated.[40]

INTERFERON GAMMA

In contrast to the use of recombinant IFN alfa, there is much less literature regarding the use of IFN gamma in systemic diseases. IFN gamma-1b (Actimmune) is the only commercially available recombinant form of IFN gamma and is approved by the FDA for the treatment of chronic granulomatous disease and osteoporosis.[3] Although there is a lack of large-scale cohort studies and trials evaluating the use of IFN gamma in patients with CTCL, there are some reports of its utility for this indication. Because there is little literature addressing IFN gamma in MF or SS, the authors' examination of the use of IFN gamma in these conditions is limited. Nevertheless, the authors' program has administered IFN gamma to more than 200 patients with MF or SS during the past 20 years and has found it to be a promising modality.

Mechanism of Action

IFN gamma has many important functions in both the innate and adaptive immune responses including, but not limited to, the stimulation of DCs and macrophages to upregulate major histocompatibility complexes leading to enhanced antigen presentation, activation of NK cells, and increasing expression of costimulatory molecules. In addition, IFN gamma is considered essential for the T_H1 immune response.[89] Researchers have postulated that many of these functions could underlie the utility of IFN gamma in MF/SS. Specifically, enhancement of cytotoxicity mediated by $CD8^+$ T cells and NK cells, priming of DCs, inhibition of tumor cell proliferation, reduced T_H2 immune activity, increased T_H1 immune activity, and inhibition of T regulatory cells are proposed mechanisms of IFN gamma's efficacy in MF/SS.[40]

Pharmacokinetics and Dosing

Like recombinant IFN alfa, recombinant IFN gamma-1b is most often administered as an SC injection in patients with MF/SS; it has also been given intralesionally but less commonly than IFN alfa in patients with MF/SS. The recommended dosage is 50 $\mu g/m^2$ (1 MU/m^2) for patients whose body surface area is greater than 0.5 m^2 and 1.5 $\mu g/kg$/dose for patients whose body surface area is equal to or less than 0.5 m^2. The mean elimination half-lives of IM and SC doses equivalent to 100 $\mu g/m^2$ are 2.9 and 5.9 hours, respectively. Peak plasma concentrations occur 4 hours after IM dosing and 7 hours after SC dosing.[90] IFN gamma injections seem to be most frequently prescribed as daily to thrice-weekly injection in patients with MF/SS. At the authors' center, typically patients are first administered 1 MU thrice weekly and then the dose is increased as tolerated to 2 MU thrice weekly.

Response to Therapy

Interferon gamma alone

The first report of using recombinant IFN gamma-1b in patients with MF/SS was published in 1990. In this prospective phase 2 study by Kaplan and colleagues,[91] 16 patients with MF/SS of various stages (IB–IVB) received recombinant IFN gamma for at least 8 weeks. The investigators reported an objective PR in 31% of patients and noted that 1 of 5 subjects with an objective PR had previously progressed after an initial PR to IFN alfa-2a. Although this study offered that IFN gamma may be effective in patients with MF or SS, its very small size and lack of control arm limited its ability to compare such efficacy to the efficacy of other treatments such as IFN alfa. The authors' group has found some success in using recombinant IFN gamma-1b in patients who have failed to respond to IFN alfa. Although on a smaller scale and via a different mechanism of IFN delivery than used by Kaplan and colleagues,[91] another trial in 2004 by Dummer and colleagues[92] also assessed the use of IFN gamma alone in subjects with CTCL. A total of 5 subjects with CTCL in this phase 1 prospective study received intralesional injections of IFN gamma complementary DNA contained in an adenoviral vector. The local intralesional injections resulted in impressive improvement of individual lesions in these patients. In addition, elevated serum levels of IFN gamma were observed, which seemed to be associated with regression of uninjected lesions.[25]

The most recent study investigating the use of recombinant IFN gamma-1b in patients with MF/SS was published in 2013 by Sugaya and colleagues.[93] This prospective phase 2 study administered IFN gamma-1b (2 MU daily for 5 days each week for 4 weeks followed by intermittent injections) to 15 patients with stage IA to IIIA CTCL. The investigators reported that 11 of 15 subjects had PRs including 9 of 10 subjects with stage IA to IIA CTCL, 1 of 4 subjects with stage IIB CTCL, and 1 of 1 subject with stage IIIA CTCL. There was no CR.

Interferon gamma as part of combination treatment

Although there are no trials comparing IFN gamma-1b directly to other CTCL treatments, several case reports and series have recorded patients with MF/SS responding to IFN gamma-1b administered in conjunction with other therapies such as bexarotene, ECP, TSEBT, and vorinostat.[74,94,95] A prospective study by Shimauchi

and colleagues[96] treated 12 patients with MF (4 with erythroderma and the rest with plaque disease) with recombinant IFN gamma or natural IFN gamma for 5 days weekly for 4 weeks in conjunction with narrowband ultraviolet B (NBUVB) therapy three times weekly. Of the 12 patients, 6 had a PR and 4 had a CR. This study also measured particular T_H1 and T_H2 cytokine levels in all 12 subjects who received the combination of IFN gamma and NBUVB and an additional 3 patients who received NBUVB alone. It was found that T_H1 chemokine levels were elevated and T_H2 chemokine levels were depressed in the combination group when compared with those receiving NBUVB alone.

The authors' center has used IFN gamma extensively as a component of multimodality treatment. The authors surmise that an advantage of IFN gamma over IFN alfa could be the former's ability to prime and enhance antigen-presenting cell functions. The authors think this could be particularly advantageous when used in conjunction with treatments such as ECP, PUVA, or TSEBT, which induce apoptosis of malignant T cells. Use of the IFN gamma can presumably enhance the afferent immune response to the apoptotic tumor cells leading to a more effective efferent immune response mediated by cytotoxic T cells.

Although not published in large case series or studies, the authors' practice has occasionally used IFN gamma and IFN alfa (usually not administering both on the same day) simultaneously in patients who have failed to achieve adequate control on a single IFN and have found that this regimen can be helpful if tolerated.

Adverse Effects

The adverse effects of IFN gamma-1b are nearly identical to those of IFN alfa. Side effects are most often flulike and include low-grade fever, myalgias, fatigue, and arthralgias. Like IFN alfa, IFN gamma can also induce nausea, headache, weight loss, dose-dependent cytopenias, liver function enzyme abnormalities, nonscarring alopecia, and the triggering of autoimmune phenomena.[91] One of the advantages cited in using IFN gamma over IFN alfa is that it does not seem to impair the cognitive or mood functions of elderly patients as often as IFN alfa.[40] The authors' group has found IFN gamma to be less frequently associated with autoimmune side effects and peripheral neuropathy than IFN alfa.

INTERFERON BETA

Although there are 2 commercially available beta-type IFNs, IFN beta-1b (Betaseron) and IFN beta-1a (Avonex), they are almost exclusively used in the treatment of multiple sclerosis so the authors summarize their attributes in an abbreviated manner. These IFNs are administered via IM or SC injections, and their side effect profile is very similar to that of IFN alfa.[12] Although there are no sizable studies or trials assessing the use of IFN beta in CTCL, a notable study is that by Zinzani and colleagues.[97] This group analyzed the use of daily IFN beta injections for 4 months in 5 patients with treatment-refractory stage III MF and 3 patients with previously untreated stage I and II MF and reported only a single OR (12.5%).[3]

TREATMENT PEARLS FOR PRESCRIBING PHYSICIANS

- It is reasonable to start nonpegylated IFN alfa, 1.5 to 3 MU, thrice weekly and increase the dose to 5 MU thrice weekly as tolerated. If the patient does not respond, increasing the frequency of the tolerated dose is an option, but the authors typically do not exceed 4 times weekly.
- Many patients experience constitutional side effects with IFNs, but these usually diminish over time. Starting at a lower dose and escalating the dose as tolerated and taking acetaminophen immediately before injection likely increase the tolerability of the drug.
- Laboratory abnormalities including cytopenias and elevated values of liver function tests can occur with IFNs, so prescribing physicians should monitor complete metabolic panels and complete blood cell counts. Mild abnormalities are typically tolerated without dose modification. If moderate or severe abnormalities occur, one should consider dose reduction or stopping the drug and referral to the appropriate specializing physician (hematologist or gastroenterologist) to address whether IFNs are contraindicated in the patient.
- Although the long-term use of IFNs seems safe, they should be used with caution in patients with history of autoimmune, mood, cognitive, and/or cardiovascular disorders.

SUMMARY

Although the available literature demonstrating the utility of recombinant IFN alfa in the treatment of CTCL is convincing, more randomized controlled trials directly comparing it both as a monotherapy and as part of combination therapy, particularly its pegylated form, to other systemic modalities used in CTCL are necessary. In addition, larger-scale studies evaluating IFN gamma both alone and in

comparison to other systemic CTCL treatments including IFN alfa would greatly enhance the understanding of its efficacy in CTCL.

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