

High-dose, high-frequency infliximab: A novel treatment paradigm for hidradenitis suppurativa



Mondana H. Ghias, BS,^a Andrew D. Johnston, MS,^a Allison J. Kutner, MD,^a Robert G. Micheletti, MD,^b H. Dean Hosgood, PhD,^c and Steven R. Cohen, MD, MPH^a
Bronx, New York and Philadelphia, Pennsylvania

Background: The permanent disfigurement associated with hidradenitis suppurativa (HS) necessitates early aggressive disease intervention. Although limited data support the use of infliximab (IFX) in HS, the efficacy of high-dose, high-frequency IFX has yet to be defined.

Objective: To evaluate the efficacy of IFX 7.5 to 10 mg/kg, with a maintenance frequency every 4 weeks.

Methods: Prospective analysis of 42 patients initiating IFX 7.5 mg/kg every 4 weeks (IFX 7.5) and 16 patients receiving dose escalation to IFX 10 mg/kg every 4 weeks (IFX 10) between March 1, 2018, and February 28, 2019. The primary outcome measure (clinical response) was the proportion of patients with Physician Global Assessment of clear, minimal, or mild (score of 0-2) HS with at least a 2-grade improvement from baseline scores.

Results: The proportion of patients achieving a clinical response after initiating IFX 7.5 was 20 of 42 (47.6%) at week 4 and 17 of 24 (70.8%) at week 12. For patients receiving dose escalation to IFX 10 because of incomplete initial response, 6 of 16 (37.5%) achieved clinical response at week 4 and 6 of 12 (50%) at week 12.

Conclusions: Initiation of IFX 7.5 every 4 weeks, with possible dose escalation to IFX 10, if needed, provides optimal mitigation of HS-related disease activity. (J Am Acad Dermatol 2020;82:1094-101.)

Key words: acne inversa; anti-TNF; anti-TNF- α therapy; biologics; hidradenitis; hidradenitis suppurativa; high dose; high frequency; infliximab; TNF inhibitor.

The pain, disfigurement, and quality-of-life impact of hidradenitis suppurativa (HS) underscore the importance of early pharmacologic intervention to improve symptoms and prevent disease progression.¹ The tumor necrosis factor (TNF) α antagonist adalimumab is currently the only biologic for HS approved by the US Food and

Drug Administration (FDA).² Several studies have reported efficacy with infliximab (IFX); however, the appropriate dose of this medication for treatment of HS is not defined.^{1,3-6}

The recommended maintenance dose and frequency of IFX for psoriasis is 5 mg/kg every 8 weeks, but the optimal therapeutic regimen for HS remains

From the Department of Internal Medicine, Division of Dermatology, Albert Einstein College of Medicine, Bronx^a; Departments of Dermatology and Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia^b; and Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx.^c

Funding sources: Mr Johnston was supported by the Albert Einstein College of Medicine Medical Scientist Training Program (NIH NIGMS T32 GM007288).

Disclosure: Dr Cohen has served as principal investigator and on the advisory board for AbbVie, Inc, and on the advisory board for Verrica Pharmaceuticals. Ms Ghias, Mr Johnston, and Drs Kutner, Micheletti, and Hosgood have no conflicts of interest to declare.

IRB approval status: Reviewed and approved by the Albert Einstein College of Medicine/Montefiore Medical Center IRB (2015-5906).

Supplemental tables and figures available at <https://doi.org/10.17632/9mhhh2zjbb.2>.

Accepted for publication September 14, 2019.

Reprint requests: Steven R. Cohen, MD, MPH, 3411 Wayne Ave, 2nd Floor, Ste D, Bronx, NY 10467. E-mail: srcohen@montefiore.org.

Published online October 4, 2019.
0190-9622/\$36.00

© 2019 by the American Academy of Dermatology, Inc.
<https://doi.org/10.1016/j.jaad.2019.09.071>

unclear. The North American Clinical HS Management Guidelines recently emphasized the need for dose-ranging studies to optimize management.³ The current FDA recommendation for adalimumab in HS doubles the loading dose and increases the maintenance frequency approved for plaque psoriasis.⁷ Furthermore, TNF- α levels in HS lesional skin were found to be 5-fold higher than the levels in psoriatic plaques.⁸ These findings underscore the high inflammatory burden in HS.^{8,9}

The IFX FDA recommendations include dose escalation up to 10 mg/kg for rheumatoid arthritis and Crohn's disease and interval frequencies as often as every 4 weeks for rheumatoid arthritis.¹⁰ Moriarty et al¹¹ attributed greater efficacy of IFX every 4 weeks in HS to neutralizing the wearing-off effects reported with longer treatment intervals.¹¹ The increased inflammatory burden in HS relative to psoriasis,^{8,9} in conjunction with a 9.5-day IFX half-life,¹² may explain the suboptimal efficacy of lower dosing and longer treatment intervals.

Persistent inflammatory activity and purulent drainage observed in the majority of patients with HS at our treatment center receiving IFX 5 mg/kg (IFX 5) led us to investigate the efficacy of high-dose, high-frequency therapy for moderate to severe HS, initiating at IFX 7.5 mg/kg every 4 weeks (IFX 7.5) or, as needed, implementing a dose escalation to IFX 10 mg/kg every 4 weeks (IFX 10) for incomplete response.

METHODS

Study design

All research activities were conducted with approval of the Albert Einstein College of Medicine institutional review board. Patients initiating IFX for HS received an induction dose of 7.5 mg/kg at weeks 0, 2, and 6, followed by a maintenance dose of 7.5 mg/kg every 4 weeks. Dose escalation to IFX 10 mg/kg was considered after completion of the induction dose for patients with insufficient disease control, defined by an HS Physician Global Assessment (HS-PGA) of moderate or worse HS (score ≥ 3).⁷ The efficacy of high-dose, high-frequency IFX was based on validated clinical measures, HS Physician Global Assessment

(HS-PGA)⁷ and Numerical Rating Scale (NRS) for pain (range, 0-10).¹³

The 6-stage outcome measure, HS-PGA, was defined as follows:

- 0, clear
- 1, minimal: noninflammatory nodules
- 2, mild: fewer than 5 inflammatory nodules or 1 abscess/draining fistula with no inflammatory nodules
- 3, moderate: 5 or more inflammatory nodules, or 1 abscess/draining fistula and at least 1 inflammatory nodule, or 2 to 5 abscesses/draining fistulas and fewer than 10 inflammatory nodules
- 4, severe: 2 to 5 abscesses/draining fistulas and at least 10 inflammatory nodules
- 5, very severe: more than 5 abscesses/draining fistulas⁷

CAPSULE SUMMARY

- Infliximab has reported efficacy in the management of moderate to severe hidradenitis suppurativa (HS), but the optimal dosage remains unclear.
- High-dose, high-frequency infliximab, initiated at 7.5 mg/kg every 4 weeks, with optional dose escalation to 10 mg/kg for inadequate disease control, provides significant reduction in HS disease activity and pain.

The patient-reported NRS for pain is an 11-point NRS ranging from 0 (no pain) to 10 (worst pain imaginable).¹³

Treatment efficacy was evaluated at weeks 4 and 12 for patients initiating IFX 7.5 or receiving dose escalation to IFX 10. The primary outcome measure was the proportion of patients with successful clinical response, as defined by an HS-PGA of clear, minimal, or mild (score of 0-2) and at least a 2-grade improvement from baseline.⁷ Secondary outcome measures included (1) the proportion of patients with an HS-PGA of clear, minimal, or mild at weeks 4 and 12; (2) mean HS-PGA score at weeks 0, 4, and 12; (3) mean NRS pain score at weeks 0, 4 and 12; and (4) the proportion of patients achieving a minimum clinically important difference (MCID) in NRS pain scores at weeks 4 and 12. MCID, defined as 30% or greater reduction and at least a 1-point decrease in NRS pain scores, was performed for patients with baseline NRS pain scores of 3 or greater.¹³⁻¹⁵

Patient selection and data collection

We established a prospective clinical cohort presenting to the Montefiore Medical Center with a diagnosis of HS (based on International Classification of Diseases, ninth revision [705.83] and International Classification of Diseases, tenth revision [L73.2] codes) and IFX treatment from March 1, 2018 through February 28, 2019. Looking Glass Clinical Analytics (Streamline Health, Atlanta,

Abbreviations used:

BMI:	body mass index
HS:	hidradenitis suppurativa
IBD:	inflammatory bowel disease
IFX:	infliximab
IFX 5:	infliximab 5 mg/kg
IFX 7.5:	infliximab 7.5 mg/kg every 4 weeks
IFX 10:	infliximab 10 mg/kg every 4 weeks
MCID:	minimum clinically important difference
NRS:	Numerical Rating Scale
PGA:	Physician Global Assessment
SAE:	serious adverse event

GA) was used to extract data from electronic medical records within the Montefiore Medical Center hospital system. Patient demographics (age, sex, race, and body mass index [BMI]); concurrent medications; initial Hurley stage; disease severity (HS-PGA); NRS pain scores; and the dates, dose, and number of IFX infusions before follow-up visits were documented. Patients included in the study fulfilled the following diagnostic criteria for HS: history of recurrent painful and/or purulent lesions localized to apocrine gland-bearing skin (at least twice in the last 6 months) and clinical presentation of nodules, abscesses, cysts, tunnels, and/or scarring of intertriginous areas.^{16,17} All patient and infusion center notes were reviewed for serious adverse events (SAEs).

Statistical analysis

Nonparametric analyses were performed with the Wilcoxon signed-rank test to evaluate change in HS-PGA and NRS pain scores at weeks 4 and 12 compared with baseline for the IFX 7.5 and IFX 10 cohorts. We examined factors influencing the primary and secondary outcomes of the combined cohorts by using binomial regression with covariates for age, sex, BMI, number of infusions (at weeks 4 and 12, accordingly), concurrent medications (anti-androgen therapy and oral antibiotics), current smoking status, and initial PGA or NRS pain score. Categorical data were evaluated for their association with dose escalation by using the chi-square test or Fisher's exact test when appropriate. All analyses were performed using R (version 3.5.1).¹⁸

RESULTS

High-dose, high-frequency IFX-HS prospective cohort

Between March 1, 2018, and February 28, 2019, patients with HS who had either never received IFX treatment or for whom treatment with IFX 7.5 mg/kg had failed were identified and enrolled into the IFX 7.5 and IFX 10 cohorts, respectively (Fig 1). Baseline

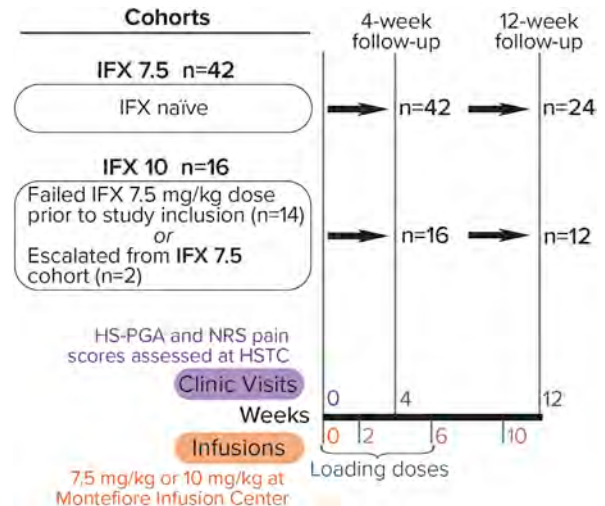


Fig 1. IFX-HS cohort dose and frequency regimens. We prospectively followed 2 sets of patients recruited from the Hidradenitis Suppurativa Treatment Center. The cohort initiated on IFX 7.5 mg/kg every 4 weeks (IFX 7.5) consisted of 42 patients with follow-up visits at week 4; 24 of these patients completed the week 12 follow-up. The other cohort was composed of 16 patients with inadequate disease control on IFX 7.5 (defined by HS-PGA \geq 3) who received dose escalation to IFX 10 mg/kg every 4 weeks (IFX 10) with follow-up at week 4; 12 patients completed the week 12 follow-up. *HS*, Hidradenitis suppurativa; *HSTC*, Hidradenitis Suppurativa Treatment Center; *IFX*, infliximab; *NRS*, Numerical Rating Scale; *PGA*, Physician Global Assessment.

and follow-up outcome measures were recorded for 42 patients initiating IFX 7.5 and 16 patients receiving dose escalation to IFX 10. Characteristics of each cohort, including demographic data, disease severity, concurrent medications, and IFX dosing regimens, are detailed in Table I.

The patients in the IFX-HS cohort were 55.3% female, with a mean age of 34.5 ± 11.9 years and mean BMI of 34.1 ± 7.1 kg/m². The average number of infusions before the week 4 and week 12 follow-up visits was 1.8 ± 0.5 , and 4.1 ± 0.9 , respectively. In accordance with the treatment algorithm implemented at our HS Treatment Center, most patients treated with IFX were concurrently prescribed topical antibiotics (98.8%), oral antibiotics (91.0%), and anti-androgen therapy (85.7%) based on the medication doses and frequencies detailed in Table I. No known SAEs were identified from the medical records of patients in the IFX-HS cohort. One patient discontinued treatment after developing myalgia and influenza-like symptoms. Overall, treatments were well tolerated across the IFX-HS cohort, with minimal safety issues to date.

Table I. Patient characteristics of the high-dose, high-frequency IFX-HS cohort at the Albert Einstein College of Medicine/Montefiore Medical Center Hidradenitis Suppurativa Treatment Center

Characteristics	IFX 7.5 mg/kg every 4 weeks	IFX 10 mg/kg every 4 weeks
Total, n	42	16
Sex, n (%)		
Male	18 (42.9)	8 (50.0)
Female	24 (57.1)	8 (50.0)
Age, years		
Range	15-57	20-67
Mean ± SD	33.3 ± 10.1	37.2 ± 15.5
BMI, kg/m ²		
Mean ± SD	33.9 ± 5.4	34.5 ± 9.5
Hurley stage, n (%)		
II	1 (2.4)	0 (0.0)
III	41 (97.6)	16 (100.0)
Race, n (%)		
African American	10 (23.8)	8 (50.0)
White	3 (7.1)	2 (12.5)
Other	16 (38.1)	4 (25.0)
Unavailable/declined	13 (31.0)	2 (12.5)
Concurrent medications, n (%)		
Topical antibiotics*	42 (100.0)	16 (100.0)
Oral antibiotics [†]	37 (88.9)	16 (100.0)
Anti-androgen [‡]	36 (85.7)	14 (87.5)

BMI, body mass index; IFX, infliximab; SD, standard deviation.

*Chlorhexidine wash, clindamycin gel (1%).

[†]Clindamycin 300 mg and rifampin 300 mg twice daily; or levofloxacin 500 mg daily, rifampin 300 mg twice daily, and metronidazole 500 mg 3 times per day.

[‡]Spironolactone 25-100 mg twice daily or finasteride 5 mg daily.

We examined the potential association of patient characteristics (age, sex, BMI, smoking status, and concurrent medications) and response to treatment. For patients in the IFX 7.5 and IFX 10 cohorts, there was a significant relationship between the primary outcome (achieving HS-PGA score of 0-2 with at least a 2-point decrease) and sex at week 4. Specifically, men were 4 times more likely to achieve the primary outcome than women (95% confidence interval, 1.09-14.62; $P = .03$). There was no significant relationship between therapeutic response and sex at week 12. We observed no relationships between the primary or secondary outcomes and age, BMI, number of infusions, smoking status, or concurrent medications.

IFX 7.5 every 4 weeks significantly reduces disease burden

Patients initiated on IFX 7.5 had a significant reduction in HS-PGA from week 0 to week 4 ($n = 42$, $P < .001$) and from week 4 to week 12 ($n = 24$,

$P < .001$) (Fig 2, B). Mean HS-PGA at weeks 0, 4, and 12 were 4.2, 2.4, and 1.8, respectively. The proportions of patients achieving clinical responses at weeks 4 and 12 were 20 of 42 (47.6%) and 17 of 24 (70.8%), respectively.

Secondary efficacy outcomes are detailed in Supplemental Table I (available at doi: [10.1016/j.jaad.2017.09.022](https://doi.org/10.1016/j.jaad.2017.09.022)). The proportions of patients with HS-PGA of clear, mild, or moderate (score of 0-2) at weeks 4 and 12 were 24 of 42 (57.1%) and 19 of 24 (79.2%), respectively. NRS pain scores decreased significantly from week 0 to week 4 ($P < .001$) (Fig 2, C) with sustained improvement at week 12 ($P < .001$) (Fig 2, C). Mean NRS pain scores at weeks 0, 4, and 12 were 5.7, 1.3, and 0.5, respectively. Of patients with baseline NRS pain scores of 3 or greater, the proportion who achieved the MCID for pain at weeks 4 and 12 was 31 of 35 (88.6%) and 21 of 22 (95.5%), respectively. Two thirds of patients (28/42) had complete resolution of pain within 4 weeks of initiating treatment.

Dose escalation to IFX 10 after inadequate control on IFX 7.5 improves outcomes

Of the 16 patients prospectively followed after dose escalation from IFX 7.5 to IFX 10, HS-PGA scores significantly decreased from week 0 to week 4 ($P < .001$) (Fig 3, A), with sustained efficacy at week 12 (Fig 3, B). Mean HS-PGA scores at weeks 0, 4, and 12 were 4.0, 2.4, and 2.3, respectively. The proportions of patients achieving clinical response at weeks 4 and 12 were 6 of 16 (37.5%) and 6 of 12 (50.0%), respectively. The proportion of patients with HS-PGA of clear, mild, or moderate at weeks 4 and 12 was 9 of 16 (56.3%) and 10 of 12 (83.3%), respectively. NRS pain scores significantly decreased from week 0 to week 4 ($P = .002$) (Fig 3, C), with continued efficacy at week 12 (Fig 3, D). Mean NRS pain scores at weeks 0, 4, and 12 were 4.3, 1.7, and 0.8, respectively. Of patients with baseline NRS pain scores of 3 or greater, the proportion who achieved the MCID for pain at weeks 4 and 12 was 9 of 11 (81.2%) and 6 of 7 (85.7%), respectively.

DISCUSSION

High-dose, high-frequency IFX significantly mitigated both HS-related disease activity and pain during the initial 4 weeks of treatment, with sustained efficacy at week 12. The results of this study suggest that initiation of IFX 7.5 with potential dose escalation to IFX 10 may optimize HS disease control.

It is of considerable interest that a 16-week randomized trial for weekly adalimumab in HS showed that 9 of 51 (17.6%) patients achieved a clinical response, using the same primary outcome as

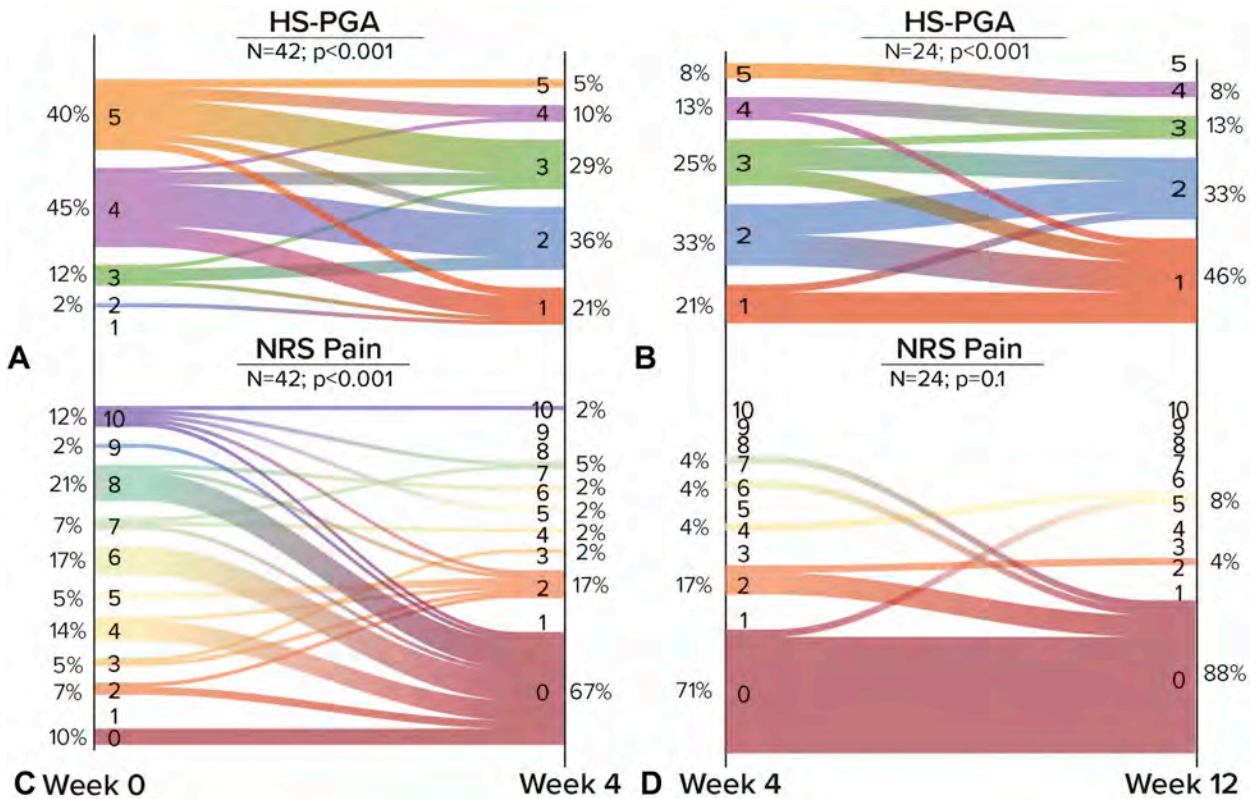


Fig 2. HS-PGA and NRS pain score improvement for patients initiated on IFX 7.5 mg/kg every 4 weeks. Riverplot diagram following individual patient response after initiating IFX 7.5 mg/kg, from weeks 0 to 4 (n = 42) and from weeks 4 to 12 (n = 24). Patients had significant improvement in (A) HS-PGA and (C) NRS pain from baseline to week 4 ($P < .001$). There was also (B) significant improvement in HS-PGA from weeks 4 to 12 ($P < .001$) and (D) sustained improvement in NRS pain at week 12. The majority of patients (85.7%) reported complete resolution of pain at week 12. The proportion of patients at each HS-PGA and NRS pain level is listed adjacent to the score for each time point. *HS*, Hidradenitis suppurativa; *IFX*, infliximab; *NRS*, Numerical Rating Scale; *PGA*, Physician Global Assessment.

reported in our study.⁷ By comparison, the proportion of patients initiating IFX 7.5 who achieved a clinical response was 20 of 42 (47.6%) and 17 of 24 (70.8%) at weeks 4 and 12, respectively.

The results of this prospective study support recommendations of the North American HS Guidelines, which suggest IFX dose and frequency adjustments up to 10 mg/kg every 4 to 8 weeks, based on expert experience.³ These outcomes are also consistent with other studies regarding the efficacy of high-dose and high-frequency IFX regimens for HS. In a retrospective analysis of 52 patients with HS treated with IFX conducted by Oskardmay et al,⁶ the majority of patients achieved stable dosing regimens for at least 8 weeks at 10 mg/kg every 6 weeks (n = 10) or every 8 weeks (n = 17). Additionally, Moriarty et al¹¹ reported superior outcomes with IFX 5 mg/kg every 4 weeks compared

with every 8 weeks, observing disease flares approximately 4 weeks after infusions.

Several inflammatory conditions, including rheumatoid arthritis, inflammatory bowel disease (IBD), and psoriasis, have shown greater clinical improvement with shorter intervals of IFX compared with dose escalation.¹⁹⁻²³ A pharmacokinetic analysis of IFX in IBD found greater efficacy in achieving therapeutic trough levels with interval shortening from every 8 weeks compared with dose escalation from 5 mg/kg.²⁴ Luber et al²³ also reported that increasing IFX frequency before dose escalation significantly improved treatment response and durability in the management of psoriasis. Although these findings support the therapeutic value of high-frequency IFX, high-dose IFX has also been shown to improve clinical outcomes.^{6,25,26} Shapiro et al²⁵ showed that 70% of children with severe IBD

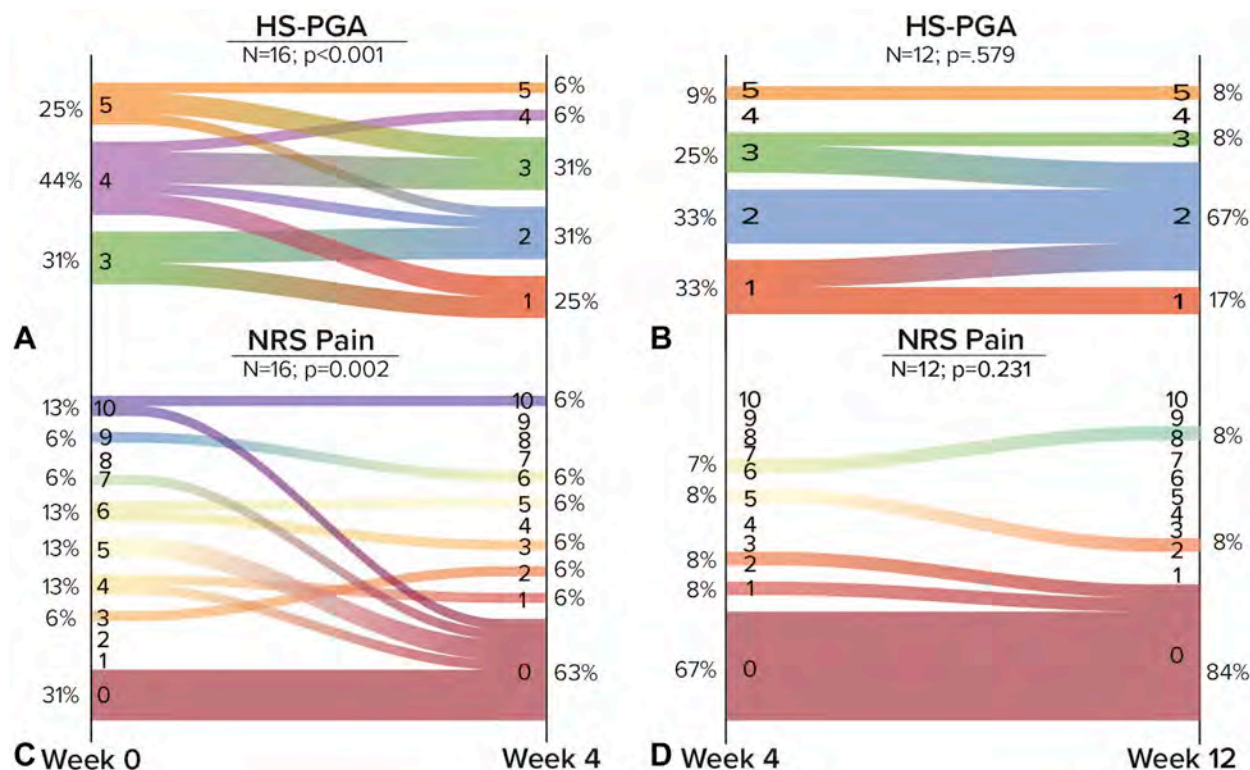


Fig 3. Patients requiring dose escalation from IFX 7.5 to IFX 10 mg/kg every 4 weeks. Riverplot diagram depicting individual patient response after dose escalation from IFX 7.5 to IFX 10 mg/kg from weeks 0 to 4 (n = 16). Patients had significant improvement in (A) HS-PGA ($P < .001$) and (C) NRS pain ($P = .002$) from baseline to week 4, with (B, D) sustained efficacy at week 12. The proportion of patients at each HS-PGA and NRS pain level is listed adjacent to the score for each timepoint. *HS*, Hidradenitis suppurativa; *IFX*, infliximab; *NRS*, Numerical Rating Scale; *PGA*, Physician Global Assessment.

required dose escalation from IFX 5, with treatment failure in 43% due to nonresponsiveness or infusion reactions. In contrast, all patients receiving high-dose IFX were able to continue therapy successfully. Given the risk of secondary loss of response to IFX over time, the first 6 to 12 months of therapy are critical for disease control, reinforcing the potential benefit of initiating IFX at higher dosing regimens for severe disease.²⁷ These studies, together with the significant improvement observed in the IFX 7.5 and IFX 10 cohorts, favor high-dose, high-frequency IFX regimens as the most effective means of optimizing HS therapeutic response.²³

A significant finding from the multivariate analysis of our study was the greater proportion of male patients achieving the primary outcome measure at week 4. There were no significant sex associations at week 12, although this may be attributed to the smaller sample size with follow-up visits at week 12. A longer observational period with more patients is necessary to confirm whether this difference is sustained. Previous studies in rheumatoid arthritis

and psoriasis also reported male sex as a positive predictor of IFX therapeutic response.²⁸⁻³³ Although the reproducibility of sex-specific differences with anti-TNF- α in other inflammatory conditions suggests a potential treatment-specific rather than disease-specific phenomenon, larger studies evaluating long-term outcomes are needed to confirm this association.

Although there was no standardized collection of safety event data, it is unlikely that many SAEs were overlooked because the majority of patients received IFX at the institutional outpatient infusion center with orders to contact the prescriber in the event of an adverse reaction. Review of all patient and infusion center notes found no documentation of SAEs. Furthermore, there is little evidence to suggest that high-dose IFX increases the risk of SAEs. In a prospective study of Crohn's disease managed with IFX, neither an increased number of total IFX infusions nor dose escalation from 5 to 10 mg/kg significantly increased the occurrence of serious infections. The relative specificity of this monoclonal

antibody ostensibly accounts for its desirable adverse effect profile.³⁴

Limitations of this study include lack of a control group or direct comparison of high-dose, high-frequency IFX to placebo or to standard IFX dosing regimens. To standardize the outcome measures, week 12 follow-up data were included for patients seen within 7 days of this designated time frame. Patient and provider scheduling limited the number of patients seen at this time point. Additionally, a few individuals had not reached the 12-week follow-up at the conclusion of the study. Although office visits and infusion notes document SAEs in the electronic medical records, some information reviewed for this study may have been lost due to recall bias.

Tunnel formation and scarring distinguish HS from other cutaneous inflammatory diseases (eg, psoriasis and atopic dermatitis) where irreversible damage is not observed. This has led to a paradigm shift in HS management from disease control to disease prevention and aggressive, early intervention.³⁵ Proactive implementation of high-dose, high-frequency IFX in the management of moderate to severe HS may not only improve clinical outcomes but also enhance patient quality of life and halt progressive disfigurement.

CONCLUSION

Patients with severe HS benefit significantly from a starting dose of IFX 7.5 mg/kg at a standard loading dose frequency (0, 2, and 6 weeks), followed by a maintenance frequency of every 4 weeks. This proposed therapeutic regimen may include a dose escalation to IFX 10 mg/kg every 4 weeks, as needed, to achieve sufficient disease and pain control. Our preliminary data affirm that high-dose, high-frequency IFX significantly improves active HS, with minimal safety issues to date. Large-scale, randomized, multicenter clinical trials are needed to confirm these promising results and optimize IFX dosing regimens and maintenance strategies for moderate to severe HS.

REFERENCES

1. Wlodarek K, Ponikowska M, Matusiak L, Szepietowski JC. Biologics for hidradenitis suppurativa: an update. *Immunotherapy*. 2019;11:45-59.
2. Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med*. 2016; 375:422-434.
3. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations. Part II: topical, intralesional, and systemic medical management. *J Am Acad Dermatol*. 2019;81:91-101.
4. Grant A, Gonzalez T, Montgomery MO, Cardenas V, Kerdel FA. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol*. 2010; 62:205-217.
5. van Rappard DC, Leenarts MF, Meijerink-van't Oost L, Mekkes JR. Comparing treatment outcome of infliximab and adalimumab in patients with severe hidradenitis suppurativa. *J Dermatolog Treat*. 2012;23:284-289.
6. Oskardmay AN, Miles JA, Sayed CJ. Determining the optimal dose of infliximab for treatment of hidradenitis suppurativa. *J Am Acad Dermatol*. 2019;81:702-708.
7. Kimball AB, Kerdel F, Adams D, et al. Adalimumab for the treatment of moderate to severe Hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med*. 2012;157:846-855.
8. van der Zee HH, de Ruiter L, van den Broecke DG, Dik WA, Laman JD, Prens EP. Elevated levels of tumour necrosis factor (TNF)-alpha, interleukin (IL)-1beta and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-alpha and IL-1beta. *Br J Dermatol*. 2011;164:1292-1298.
9. Riis PT, Soeby K, Saunte DM, Jemec GB. Patients with hidradenitis suppurativa carry a higher systemic inflammatory load than other dermatological patients. *Arch Dermatol Res*. 2015;307:885-889.
10. *Infliximab [package insert]*. Horsham, PA: Janssen Biotech Inc; 2017.
11. Moriarty B, Jiyad Z, Creamer D. Four-weekly infliximab in the treatment of severe hidradenitis suppurativa. *Br J Dermatol*. 2014;170:986-987.
12. Cornillie F, Shealy D, D'Haens G, et al. Infliximab induces potent anti-inflammatory and local immunomodulatory activity but no systemic immune suppression in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2001;15:463-473.
13. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. *J Pain*. 2003;4:407-414.
14. Grimstad O, Tzellos T, Dufour DN, et al. Evaluation of medical and surgical treatments for hidradenitis suppurativa using real-life data from the Scandinavian registry (HISREG). *J Eur Acad Dermatol Venereol*. 2019;33:1164-1171.
15. Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. *J Pain Symptom Manage*. 2003;25:406-411.
16. Zouboulis CC, Del Marmol V, Mrowietz U, Prens EP, Tzellos T, Jemec GB. Hidradenitis suppurativa/acne inversa: criteria for diagnosis, severity assessment, classification and disease evaluation. *Dermatology*. 2015;231:184-190.
17. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol*. 2015;29:619-644.
18. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018.
19. Edrees AF, Misra SN, Abdou NI. Anti-tumor necrosis factor (TNF) therapy in rheumatoid arthritis: correlation of TNF-alpha serum level with clinical response and benefit from changing dose or frequency of infliximab infusions. *Clin Exp Rheumatol*. 2005;23:469-474.
20. St Clair EW, Wagner CL, Fasanmade AA, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2002;46:1451-1459.
21. van Vollenhoven RF, Klareskog L. Infliximab dosage and infusion frequency in clinical practice: experiences in the

- Stockholm biologics registry STURE. *Scand J Rheumatol*. 2007;36:418-423.
22. Hibi T, Sakuraba A, Watanabe M, et al. Retrieval of serum infliximab level by shortening the maintenance infusion interval is correlated with clinical efficacy in Crohn's disease. *Inflamm Bowel Dis*. 2012;18:1480-1487.
 23. Luber AJ, Tsui CL, Heinecke GM, Lebowitz MG, Levitt JO. Long-term durability and dose escalation patterns in infliximab therapy for psoriasis. *J Am Acad Dermatol*. 2014;70:525-532.
 24. Dotan I, Ron Y, Yanai H, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis*. 2014;20:2247-2259.
 25. Shapiro JM, Subedi S, Machan JT, et al. Durability of infliximab is associated with disease extent in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2016;62:867-872.
 26. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology*. 2009;137:1250-1260.
 27. Puig L. Obesity and psoriasis: body weight and body mass index influence the response to biological treatment. *J Eur Acad Dermatol Venereol*. 2011;25:1007-1011.
 28. De Simone C, Caldarola G, Maiorino A, et al. Clinical predictors of nonresponse to anti-TNF-alpha agents in psoriatic patients: a retrospective study. *Dermatol Ther*. 2016;29:372-376.
 29. Esposito M, Gisondi P, Cassano N, et al. Survival rate of antitumour necrosis factor-alpha treatments for psoriasis in routine dermatological practice: a multicentre observational study. *Br J Dermatol*. 2013;169:666-672.
 30. Gniadecki R, Kragballe K, Dam TN, Skov L. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. *Br J Dermatol*. 2011;164:1091-1096.
 31. Hyrich KL, Watson KD, Silman AJ, Symmons DP, British Society for Rheumatology Biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford)*. 2006;45:1558-1565.
 32. Kleinert S, Tony HP, Krause A, et al. Impact of patient and disease characteristics on therapeutic success during adalimumab treatment of patients with rheumatoid arthritis: data from a German noninterventional observational study. *Rheumatol Int*. 2012;32:2759-2767.
 33. Kvien TK, Uhlig T, Odegard S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. *Ann N Y Acad Sci*. 2006;1069:212-222.
 34. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. *Am J Gastroenterol*. 2012;107:1409-1422.
 35. Paek SY, Hamzavi I, Danby FW, Qureshi AA. Disease modification for hidradenitis suppurativa: a new paradigm. *J Am Acad Dermatol*. 2017;76:772-773.