Determining the optimal dose of infliximab for treatment of hidradenitis suppurativa

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Background: Few data exist to guide infliximab dosing in hidradenitis suppurativa (HS).

Objectives: To determine optimal infliximab dosing for patients with HS based on treatment response and achievement of stable dosing.

Methods: Retrospective cohort study of 52 patients with HS treated with infliximab. Primary outcome was achievement of stable dosing regimen for at least 8 weeks. Secondary outcomes were time to discontinuation, time to titration, changes to inflammatory markers, and clinical response.

Results: Thirty-five patients (67%) achieved stable dosing, most at a schedule of 10 mg/kg every 6 or 8 weeks. At 1 year from initiation, most patients (64%) required dose escalation. Patients tolerated infliximab well and achieved significant improvements in abscess and nodule count, draining sinuses, and erythrocyte sedimentation rate.

Limitations: Retrospective nature and lack of HS clinical response data for many patients.

Conclusions: Infliximab 10 mg/kg every 6 or 8 weeks may be a reasonable starting dosage for most patients. (J Am Acad Dermatol 2019;81:702-8.)

Key words: clinical research; drug response; general dermatology; hidradenitis; infliximab; medical dermatology.

Hidradenitis suppurativa (HS) is a chronic inflammatory follicular disease with recurrent painful nodules and abscesses in predominantly intertriginous locations.[1,2] Pathogenesis of HS is incompletely understood, but the associations of HS with multiple chronic inflammatory disorders and elevated serum tumor necrosis factor-α point to contributions from a dysregulated immune system.[3-7] The tumor necrosis factor-α antagonists adalimumab and infliximab have shown promise in suppressing HS activity by demonstrating efficacy in treating Hurley stage II-III disease, with improvement in patient-oriented outcomes in randomized controlled trials (RCTs).[8-12]

Despite widespread use of infliximab and adalimumab, only adalimumab is currently approved by the US Food and Drug Administration for treatment of HS. Additionally, few data exist to guide dosing of infliximab in HS. In the experience of the author (CS), there is frequent need to escalate infliximab dosing to reach optimal disease control. The primary aim of this study was to retrospectively evaluate the typical infliximab dosing regimen that results in optimal disease control by using dose titration based on patient symptoms.

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METHODS

Study procedures were reviewed and approved by the university's institutional review board. This was a retrospective cohort study of 52 patients with HS treated with infliximab.

Data collection

An internal list of all patients identified as having HS and being treated at a single academic outpatient center at the University of North Carolina Department of Dermatology with infliximab maintenance dosing was compiled chronologically. Patient charts were reviewed and evaluated for inclusion. Exclusion criteria were (1) missing dosing data and (2) patients still receiving loading doses. Patients were given loading doses ranging from 5 mg/kg to 10 mg/kg based on provider preference at weeks 0, 2, and 6, and then they generally continued to receive the same dose every 8 weeks for maintenance. If patients reported inadequate control or disease flares before a maintenance dose, then the dose interval was shortened or the dose was increased in stepwise fashion based on the timing of the flare before the next dose was due. When the disease was believed to be stable with minimal activity between maintenance doses, the dose and interval would remain stable.

Data collected from the reviewed charts included patient demographics, comorbid medical conditions, time of symptom onset, time of diagnosis, time of treatment, prior medications, concomitant medications, dosing, time of dosing changes, clinical examination findings including Hurley stage and inflammatory lesion counts, results of laboratory measures of inflammation, and adverse events.

Outcomes of interest

The primary outcome was achievement of stable dosing with documented response to treatment, although specific criteria for determining response were not recorded for all patients. Dosing was considered stable when the dose and interval remained unchanged for at least 8 weeks. HS Clinical Response (HiSCR) values were calculated by using clinical data from chart reviews when available.

Secondary outcomes of interest included clinical and laboratory value improvements (abscess and nodule [AN] counts, draining sinuses, erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] and hemoglobin levels) between the initial and final time points.

Statistical analysis

We compared the proportion of patients achieving a stable infliximab dose or HiSCR across starting and final dosing regimens using the Kruskal-Wallis test. Clinical and laboratory value improvements were compared with 1-sample *t* tests. Improvements were compared between those who achieved a stable dose and those who did not by using independent-samples *t* tests. Survival analyses were performed with the Kaplan-Meier method to compare the probability of remaining on the initial dosing regimen or discontinuing infliximab. Changing prescribing methods over time, combined with the fact that many patients had initiated infliximab relatively recently, violated the assumption of independent censoring, which led to underestimated survival probabilities and made interpretation challenging. For a more suitable analysis, we included patients with at least 1 year of data and limited time at risk to 1 year from initiation.

Statistical analyses were performed using STATA, version 15 (StataCorp, College Station, TX). Fig 1 was created with an online Sankey diagram generator.[13] All tests were 2-sided. *P* values less than .05 were considered significant.

CAPSULE SUMMARY

- Infliximab is an effective treatment modality in the management of moderate to severe hidradenitis suppurativa, with dose titration often required to optimize response to treatment.
- For patients with hidradenitis suppurativa beginning treatment with infliximab, 10 mg/kg every 6 or 8 weeks may be a reasonable initial dosing regimen.

RESULTS

We identified 67 patients treated with infliximab for HS between June 2015 and March 2018. After chart review, 15 patients were excluded from further evaluation because patients were still receiving loading doses (n = 3) or were missing dosing information (n = 12). The 52 remaining charts were used to determine dosing patterns over time.

Demographic information (Table I) shows that this population is primarily in the third to fifth decade of life, had a mean symptom duration of approximately a decade, and was mostly female (73%) and African American (62%). Most patients had Hurley stage III disease (87%). Obesity was the most common comorbidity (76%), followed by depression (19%), hypertension (17%), and type 2 diabetes

Abbreviations used:

AN:	abscess-nodule count
CRP:	C-reactive peptide
ESR:	erythrocyte sedimentation rate
HiSCR:	Hidradenitis Suppurativa Clinical Response
HS:	hidradenitis suppurativa
RCT:	randomized controlled trial

(13%). On average, patients received 3.8 prior treatments, most commonly antibiotics (90%), adalimumab (85%), and surgery (67%). During the course of infliximab therapy, patients were receiving an average of 2.1 concomitant treatments, most commonly antibiotics (52%) or methotrexate (40%).

On average, these 52 patients received infliximab for 54.4 weeks (range, 3-142 weeks), for a cumulative exposure time of 48.8 years. Initial and final dosing regimens are summarized in Table II. The most common initial regimens were 10 mg/kg every 8 weeks (n = 36, 69%) and 7.5 mg/kg every 8 weeks (n = 10, 19%). At the time of data collection, 10 patients (19%) had discontinued infliximab, and the most common ongoing regimens were 10 mg/kg every 8 weeks (n = 17, 33%) and 10 mg/kg every 6 weeks (n = 14, 27%). In total, 33 patients (63%) required dose titration, and 15 (29%) discontinued. Of those who discontinued, 6 (40%) restarted, and of these, 1 patient discontinued again. An illustration of the flow of patients from initial to final dose shows how most patients required dose escalation, particularly if started at lower doses (Fig 1).

Thirty-five patients (67%) achieved the primary outcome, which is achievement of a stable dosing regimen (Table II). The proportion of patients achieving a stable dose did not differ by initial dose ($P = .94$) or final dose ($P = .25$). HiSCR was calculable for 22 patients; of those, 14 (64%) achieved a response. The proportion of patients with a HiSCR response was not significantly different by initial ($P = .09$) or final dose ($P = .87$).

A depression diagnosis was less common in patients who achieved a stable dosing regimen (9% vs 44%, respectively; $P = .003$), whereas obesity was more common in patients who achieved a stable

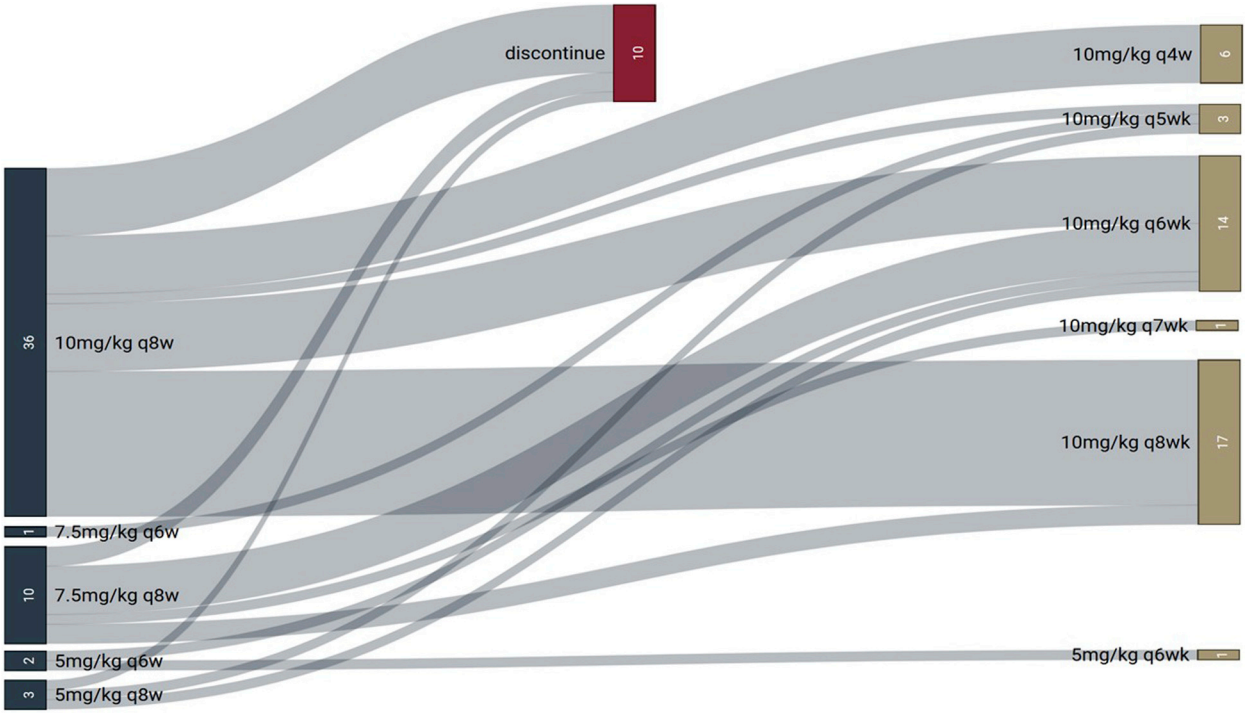

Fig 1. Sankey diagram showing the flow of 52 patients from initial to final dosing regimens. Initial regimens are listed on the left and final regimens on the right. Patients who discontinued at any point were included in the discontinue group. Higher dosing regimens are farther up on the right and left axes for qualitative demonstration and are not meant to represent a quantitative scale (eg, gray lines that are horizontal indicate no change from initial to final dosing). Developed with the Sankey Diagram Generator (http://sankey-diagram-generator.acquireprocure.com/).[13] *q*, Every; *w*, weeks; *wk*, weeks.

Table I. Descriptive statistics of 52 patients with hidradenitis suppurativa treated with infliximab

Characteristic	Total (N = 52)	Achieved stable regimen* (n = 35, 67%)	Did not achieve stable regimen (n = 17, 33%)
Age in years, mean ± SD	35.5 ± 11.4	34.6 ± 10.9	37.3 ± 12.5
Age in years at first symptoms, mean ± SD	23.5 ± 12.1	22.4 ± 11.8	25.8 ± 12.9
Female sex, n (%)	38 (73%)	26 (74)	12 (71)
Ethnicity, n (%)			
White	13 (25%)	8 (23)	5 (29)
African American	32 (62)	22 (63)	10 (59)
Other	2 (4)	2 (6)	0 (0)
Missing	5 (10)	3 (9)	2 (12)
Smoking status, n (%)			
Ever smoker	26 (50)	18 (51)	8 (47)
Never smoker	26 (50)	17 (49)	9 (53)
Hurley stage, n (%)			
II	4 (8)	4 (11)	0 (0)
III	45 (87)	31 (89)	14 (82)
Missing	3 (6)	0 (0)	3 (18)
BMI in kg/m^2, mean ± SD	37.7 ± 8.8	39.2 ± 8.8	34.4 ± 7.9
Number of comorbidities, mean ± SD	1.7 ± 0.9	1.6 ± 0.8	1.8 ± 1.0
Number of prior treatments, mean ± SD	3.8 ± 1.2	3.8 ± 1.2	3.7 ± 1.2
Adalimumab, n (%)	44 (85)	28 (80)	15 (94)
Antibiotics, n (%)	47 (90)	33 (94)	13 (81)
Surgery, n (%)	35 (67)	22 (63)	12 (75)
Number of concomitant treatments, mean ± SD	2.1 ± 1.4	2.1 ± 1.4	2.2 ± 1.6
Antibiotics, n (%)	27 (52)	18 (51)	9 (56)
Methotrexate, n (%)	21 (40)	14 (40)	7 (44)
Steroids, n (%)	19 (37)	11 (31)	8 (50)
Receiving infliximab only, n (%)	6 (12)	3 (9)	3 (18)
Weeks receiving infliximab (mean ± SD)	54.4 ± 34.9	55.3 ± 34.7	52.3 ± 36.2
Adverse events, n (%)	13 (25)	7 (20)	6 (35)

BMI, Body mass index; *SD*, standard deviation.
*Indicates that patient is actively taking drug without dose alterations for at least 8 weeks.

dosing regimen than in those who did not (86% vs 60%, respectively; $P = .05$). Other comorbid conditions, such as diabetes, hypertension, pyoderma, inflammatory arthritis, Crohn's disease, and psoriasis, did not significantly differ between groups. No measured demographic characteristics were statistically different between those who achieved a stable dosing regimen and those who did not.

There were significant improvements in mean AN count, draining sinuses, ESR, and hemoglobin level, but not CRP level (Table III). Stratification by outcome showed similar improvements, except for CRP level, which was improved in the group achieving stable dosing and worse in the group that did not ($P = .03$). Additionally, those who did not achieve stable dosing still saw improvements in AN count and draining sinuses, but not in laboratory values (ESR, CRP, or hemoglobin).

Twenty-five patients (48%) initiated infliximab more than 1 year before data collection and thus were included in survival analyses. A survival analysis of those remaining on their initial dose showed 50% of patients remaining on their initial dose at 25.7 weeks and 5 patients (20%) remaining on their initial dose at 52 weeks (Fig 2, *A*). A survival analysis of those remaining on infliximab showed 21 patients (84%) remaining on infliximab after 52 weeks (Fig 2, *B*). At 1 year from initiation, 16 patients (64%) required dose escalation, 3 (12%) had discontinued infliximab, and 1 was lost to follow-up.

Overall, infusions were well tolerated, with 10 patients (19%) experiencing a total of 12 adverse events, which were mostly mild. Adverse events were mucocutaneous infections (n = 4), chest pain (n = 2), influenza-like symptoms (n = 2), pruritus (n = 1), photosensitivity (n = 1), and an exposed fetus (n = 1). One patient with obesity and diabetes was given a diagnosis of sepsis. The rate of adverse events did not significantly differ based on initial ($P = .75$) or final ($P = .70$) infliximab dose. Fifteen patients discontinued infliximab, of whom 12 had recorded reasons. One patient temporarily discontinued because of abscess development, and 1 permanently discontinued because of pregnancy.

Table II. Initial and final dosing regimens of participants stratified by primary outcome measure

	All participants (N = 52), n (%)*		Participants achieving stable dosing regimen,† (n = 35, 67%), n^{stable}/n^{total} (%)‡		Participants achieving positive HiSCR§ (n = 14, 64%), n^{HiSCR}/n^{total} (%)‡	
Dose	**Initial**	**Final**	**Initial**	**Final**	**Initial**	**Final**
10 mg/kg q4w	—	6 (12)	—	3/6 (50)	—	2/4 (50)
10 mg/kg q5w	—	3 (6)	—	3/3 (100)	—	0/1 (0)
10 mg/kg q6w	—	14 (27)	—	10/14 (71)	—	4/6 (67)
10 mg/kg q7w	—	1 (2)	—	1/1 (100)	—	—
10 mg/kg q8w	36 (69)	17 (33)	24/36 (67)	17/17 (100)	13/18 (72)	6/9 (67)
7.5 mg/kg q6w	1 (2)	—	1/1 (100)	—	0/1 (0)	—
7.5 mg/kg q8w	10 (19)	—	7/10 (70)	—	0/2 (0)	—
5 mg/kg q6w	2 (5)	1 (2)	1/2 (50)	1/1 (100)	—	—
5 mg/kg q8w	3 (6)	—	2/3 (67)	—	1/1 (100)	—
Discontinued	—	10 (19)	—	0/10 (0)	—	2/2 (100)‖

HiSCR, Hidradenitis Suppurativa Clinical Response; *q*, every; *w*, weeks.
*Percentages represent proportion out of all participants.
†A patient was considered to be stable when dosing regimen remained constant for at least 8 weeks.
‡Percentages represent proportion of participants within a dosing category.
§A positive HiSCR defined as at least 50% fewer abscesses and nodules, with no increase from baseline abscesses or fistulae. Data for HiSCR were available for only 22 participants; thus, denominators do not match values in the "All Participants" columns.
‖The 2 patients who had discontinued infliximab at the time of data collection despite having a positive response based on HiSCR criteria discontinued because of either loss of insurance coverage or issues with the infusion center.

Table III. Improvements over study period for total sample (n = 52) and stratified by primary outcome

	Total (N = 52)			Achieved stable regimen* (n = 35)			Did not achieve stable regimen (n = 17)			Between-group difference
Clinical and laboratory measurements	**n†**	**Improvement mean (SD)**	***P* value‡**	**n†**	**Improvement mean (SD)**	***P* value‡**	**n†**	**Improvement mean (SD)**	***P* value‡**	***P* value§**
AN count	23	7.2 (9.2)	**.001**	17	5.4 (7.9)	**.01**	6	12.3 (11.5)	**.05**	.11
Draining sinuses	25	5.8 (5.5)	**<.001**	18	5.8 (4.3)	**<.001**	7	5.8 (6.0)	**.01**	.99
ESR, mm/h	39	8.1 (21.8)	**.03**	26	11 (22.0)	**.02**	13	2.2 (20.9)	.72	.24
CRP, mg/L‖	39	-0.3 (17.1)	.92	27	3.6 (14.1)	.20	12	-9.0 (20.6)	.16	**.03**
Hemoglobin, g/dL	42	0.4 (1.2)	**.04**	28	0.6 (1.0)	**.004**	14	0.1 (1.5)	.91	.18

AN, Abscess and nodule; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *SD*, standard deviation.
*Stable indicates that patient has been actively taking drug without dose alterations for at least 8 weeks.
†Count may not sum to total because of missing data.
‡*P* values obtained via 1-sample *t* test using 0 as the null. Bold type indicates significant *P* value at the <.05 level.
§*P* values obtained via independent-samples *t* test. Bold type indicates significant *P* value at the <.05 level.
‖A single observation was excluded as an outlier for this analysis.

The remaining 10 reasons were infusion center issues (n = 4), loss of insurance (n = 2), poor control of disease (n = 2), development of anti-infliximab antibodies (n = 1), and cost (n = 1).

DISCUSSION

All but 1 in the 52-patient cohort ended the study period at a dosage of 10 mg/kg every 8 weeks or greater if they were still taking infliximab. Of the 35 patients (67%) who achieved a stable regimen, nearly half were receiving a dosage of 10 mg/kg every 8 weeks. Significant improvements over our study period were seen in mean AN count, draining sinuses, and ESR. The 22 patients with available HiSCR data showed patterns similar to our stable outcome, with 14 (64%) having a positive response. These response rates are similar to each other and to those reported in the literature.[14]

To our knowledge, this is the largest reported cohort of patients with HS treated with infliximab. It also incorporates higher dosing regimens and has a relatively long study duration. A recent review of biologic therapy in HS found 9 cohort studies (2003-2012, 64 total patients) and a single RCT (2010) examining infliximab.[15] The RCT was the largest individual study, with 38 patients with HS, 15 of whom received infliximab at 5 mg/kg every 8 weeks. Twenty-six percent of patients in the treatment arm

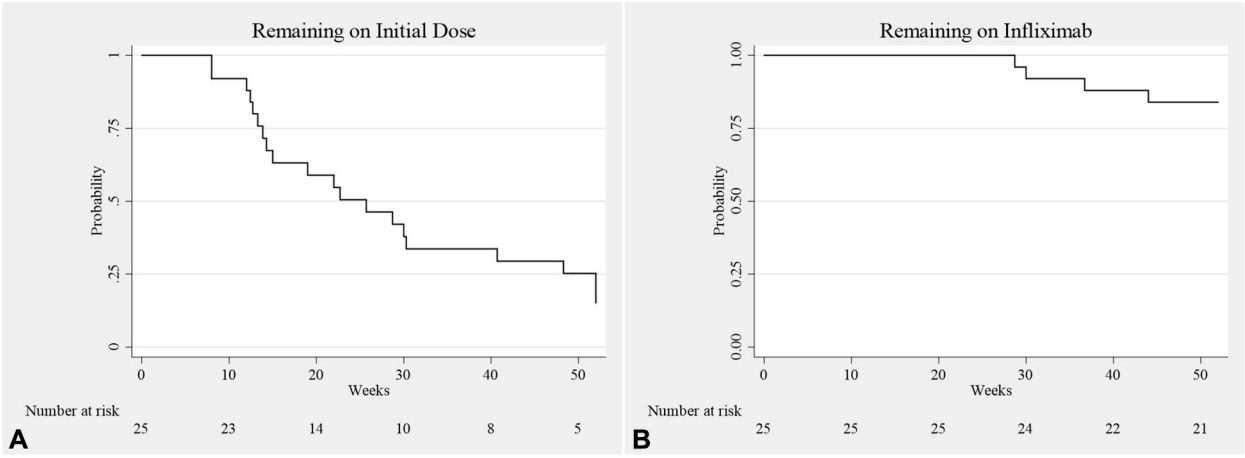

Fig 2. Kaplan-Meier curves of patients during the first year after initiating maintenance dosing of infliximab. **A**, Probability of patients remaining on initial maintenance dosing. **B**, Probability of patients remaining on infliximab at any dosing regimen.

experienced a greater than 50% reduction in HS Severity Index score, and 60% experienced 25% to 50% improvement in disease activity.[8] Most of the cohort studies examined HS response to doses of 5 mg/kg, with the exception of 1 study in which doses ranging from 5 to 10 mg/kg were used. Some studies assessed responses only after induction infusions at weeks 0, 2, and 6, whereas the studies using maintenance therapy reported postinduction dosing intervals ranging from every 4 to 8 weeks.[8-12,15,16]

For most inflammatory conditions, manufacturer-recommended maintenance regimens of infliximab are 5 mg/kg every 8 weeks, with doses up to 10 mg/kg and frequencies of up to every 4 weeks recommended for certain refractory cases of rheumatoid arthritis and Crohn's disease.[17] Likely because of this precedent, most prior studies of infliximab for HS have examined dosages of 5 mg/kg dosed every 8 weeks,[10,15,17] with 1 study suggesting that 5 mg/kg every 4 weeks is relatively superior.[11] Our study provides additional evidence for the use of higher dosing regimens when using infliximab in HS, most commonly 10 mg/kg every 8 weeks (n = 17, 49%) or every 6 weeks (n = 10, 29%).

Limitations of our study are the retrospective design and the potential for limited generalizability because the included patients had severe HS and were from a single medical center. Treatment was determined by clinical practice patterns of the primary investigator and was not subject to a predetermined protocol. Assessment of disease response with a previously reported measure (HiSCR) was not available for many patients because of insufficient data. Strengths of our study include sample size, which is relatively large in the context of existing HS literature, and the fact that our results are similar to those seen using available HiSCR data within our cohort and to those of other smaller reports in the literature.

In conclusion, our results suggest that for most patients with HS, treatment with infliximab will likely be optimized at a dosage at or greater than 10 mg/kg every 8 weeks and that lower starting regimens are unlikely to be maintained because of inadequate disease response. Author experience during the study resulted in very few patients starting on doses less than 10 mg/kg every 8 weeks because the disease routinely flared within 4 to 6 weeks of each dose. Starting patients on an initial dosing of 10 mg/kg every 8 weeks has the potential to reduce the number of adjustments needed to achieve a stable dosing regimen with good clinical response. The results also suggest that a significant proportion of patients may require dosing of 10 mg/kg every 6 weeks or even every 4 weeks over time to maintain an adequate response. Because most previous studies have examined HS responses to infliximab dosages of 5 mg/kg at varying time intervals, further research is needed to characterize the adverse effect profile of higher dosages for HS, although it was tolerated well with few serious adverse events in this study population. More data are also necessary to determine which patients might benefit from higher or lower infliximab dosages.

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