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ORIGINAL ARTICLES

Hidradenitis Suppurativa. Response to Treatment With Infliximab

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Abstract. *Introduction.* Hidradenitis suppurativa is a chronic inflammatory disease that runs in outbreaks with painful lesions, fistulas and scars in axillae, groins, buttocks, and perianal and submammary regions. Among multiple drug therapies available, infliximab, usually employed in dermatology to control psoriasis, has shown its efficacy in the past five years.
Patients and method. It is a prospective, observational study to determine the efficacy and safety of infliximab in the treatment of hidradenitis suppurativa. We selected three women with a history of hidradenitis suppurativa of more than 10 years, with involvement of at least two anatomic locations that was recalcitrant to conventional therapies. Each patient received infliximab at a dose of 5mg/kg/infusion on weeks 0, 2, 6 and every 8 weeks thereafter.
Results. Two of the three patients showed mild to moderate improvement of their disease while the third patient did not improve. We can highlight the variability of the results observed in these three patients. Adverse effects were generally mild and well tolerated by the three patients. Despite this, two patients withdrew the therapy due to loss of efficacy in one case and the development of generalized arthalgias in the other case.
Conclusions. Treatment of hidradenitis supurativa with infliximab constitutes a moderately useful alternative in some cases.

Key words: tumor necrosis factor, hidradenitis suppurativa, infliximab.

HIDROSADENITIS SUPURATIVA. RESPUESTA AL TRATAMIENTO CON INFLIXIMAB

Resumen. *Introducción.* La hidrosadenitis supurativa es una enfermedad inflamatoria crónica, que cursa en brotes, con lesiones dolorosas, fístulas y cicatrices en axilas, ingles, glúteos, región perianal e inframamaria. Entre los múltiples tratamientos farmacológicos disponibles, en los últimos cinco años se ha demostrado la eficacia del infliximab, un tratamiento habitualmente utilizado en dermatología para el control de la psoriasis.
Pacientes y método. Estudio prospectivo, observacional, realizado con el objetivo de determinar la eficacia y seguridad del infliximab en el tratamiento de la hidrosadenitis supurativa. Tres pacientes mujeres con hidrosadenitis supurativa de más de 10 años de evolución, con afectación de al menos dos localizaciones anatómicas y resistente a terapias convencionales. Se realiza tratamiento con infliximab a cada una de las pacientes en dosis de 5 mg/kg/infusión en las semanas 0, 2, 6 y posteriormente cada 8 semanas.
Resultados. Dos de las tres pacientes presentaron una mejoría leve-moderada de su enfermedad, mientras que la tercera paciente no obtuvo mejoría. Podemos destacar la variabilidad de los resultados observada entre las tres pacientes. Los efectos secundarios fueron en general leves y bien tolerados por las tres pacientes. Pese a ello, dos de las pacientes tuvieron que suspender el tratamiento debido a la falta de eficacia del mismo en uno de los casos y a un cuadro de artralgias generalizadas en otro.
Conclusiones. El tratamiento de la hidrosadenitis supurativa con infliximab constituye una alternativa moderadamente útil en algunos casos.

Palabras clave: factor de necrosis tumoral, hidrosadenitis supurativa, infliximab.

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Introduction

Hidradenitis suppurativa is a chronic inflammatory disease with a clinical course characterized by recurrences of very painful abscesses and nodules with an unpleasant smell,

along with sinus tract formation and scarring. The disease affects mainly the axillae, groin, buttocks, and perianal and inframammary regions (all parts of the body with a high density of apocrine glands). The disease usually presents initially during puberty and is slightly more common in women. It is usually associated with deterioration in the quality of life of the patient, who may become frustrated and depressed, and suffer social isolation and relationship problems. A variety of therapeutic options are available, such as general interventions (weight loss and smoking cessation), pharmacological interventions (antibiotics, isotretinoin, finasteride, prednisone, cyclosporine, etc), surgery (incision and drainage, healing by secondary intention, etc), and other types of intervention (carbon dioxide laser therapy and radiotherapy). In the last 5 years, the efficacy of infliximab has been demonstrated. This chimeric monoclonal antibody acts by inhibiting the proinflammatory effects of tumor necrosis factor alpha (TNF-α).[1] Its efficacy has been demonstrated in a number of dermatological diseases, including psoriasis.[2,3] We present 3 patients with long-standing active hidradenitis suppurativa resistant to conventional therapy who were treated with infliximab.

Patients and Methods

We selected 3 patients with a history of more than 10 years of hidradenitis suppurativa and involvement of at least 2 anatomical sites. In all cases, the disease had been resistant to multiple previous treatments. The baseline characteristics of the patients are shown in Table 1.

Before starting treatment with infliximab, a series of complementary tests were done that included complete blood counts; determination of blood glucose, urea, creatinine, electrolytes, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, alkaline phosphatase, complete urinalysis, antinuclear antibodies (ANA), anti-extractable nuclear antigen antibodies, and nuclear localizing anti-DNA antibodies; serological tests for the hepatitis B, hepatitis C, and human immunodeficiency viruses; tuberculin test; and chest radiograph.

Infliximab was administered as an intravenous infusion to each patient at a dose of 5 mg per kilogram body weight per infusion at weeks 0, 2, and 6 and then every 8 weeks. The same dose was maintained throughout the study.

The following variables were determined for each patient at the time of each of the infusions:

1. Number, site, and characteristics of the lesions (inflammatory, suppurative, scarring)
2. Severity of symptoms (assessed subjectively by the physician): mild, moderate, severe
3. Frequency of recurrences (number of recurrences per month)
4. Subjective assessment of the disease by the patient on an analogue scale of 0 to 10, with 10 corresponding to the worst state

Table 1. Baseline Characteristics of the 3 Patients

No./Age/Sex	*Duration of Hidradenitis Suppurativa, y*	*Lesion Site*	*Prior Treatments*	*Medical History*	*Complementary tests*
1/28/Woman	13	Axillae, groin	Topical and systemic antibiotics (clindamycin) Nonsteroidal antiinflammatory drugs Systemic corticosteroids, isotretinoin Oral contraceptives Pilonidal sinus surgery (4 times)	Dyslipidemia	Normal or negative
2/29/Woman	15	Axillae, pubis, groin, buttocks, submammary region	Oral antibiotics (doxycycline, cloxacillin, clindamycin) Systemic corticosteroids Multiple surgical drains	Morbid obesity	Normal or negative
3/41/Woman	15	Groin, buttocks	Topical (mupirocin) and systemic (clindamycin, tetracyclines) antibiotics		
negative			Systemic corticosteroids Isotretinoin Oral contraceptives	Not relevant	Normal or

5. Self-rated analogue overall quality-of-life score (EuroQol instrument), which ranges from 0 to 100, with 100 corresponding to the worst state
6. Subjective assessment by the patient of the degree of discomfort from symptoms (pain, pruritus, etc) on an analogue scale of 0 to 10, with 10 corresponding to the worst state
7. Side effects
8. Skin-disease–specific quality-of-life score (Skindex-29), with higher percentages corresponding to poorer quality of life. This instrument for measuring quality of life was developed by Dr MM Chen[4] in the United States of America, and adapted for Spanish speakers by Dr M Jones-Cabellero.[5] It assesses 3 dimensions or domains (emotional, functional, and symptoms) with 28 items or questions.
9. Overall treatment satisfaction on an analogue scale of 0 to 10, with 10 corresponding to maximum satisfaction and 0 to greatest dissatisfaction

The skin-disease–specific quality-of-life test was only administered at the baseline visit and at the third infusion of infliximab (sixth week) and treatment satisfaction was only assessed at the third infliximab infusion.

In addition, at each infusion, laboratory tests including complete blood counts, glucose, urea, creatinine, electrolytes, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, and alkaline phosphatase were performed.

Results

The results for the 3 study patients are presented in Tables 2, 3, and 4 and in Figures 1, 2, and 3. A large variability was apparent in our patients. Patient 1 improved—the number of inflammatory and suppurative lesions and the frequency of recurrences decreased. Therefore her overall disease severity decreased. This patient suffered a mild recurrence of hidradenitis during the last 2 infusions of infliximab. We interpreted this as a decrease in efficacy over time. Figure 2 shows the clinical improvement of this patient with treatment. Subjectively, however, the patient considered her state to be similar to that before treatment (subjective hidradenitis scale), with the same quality of life (EuroQol instrument, Skindex-29), although she was in less discomfort (hidradenitis discomfort scale). In general, this patient was dissatisfied with treatment despite objective clinical

Table 2. Results for Patient 1

Patient 1	*1st Infusion (0 Weeks)*	*2nd Infusion (2 Weeks)*	*3rd Infusion (6 Weeks)*	*4th Infusion (14 Weeks)*	*5th Infusion (22 Weeks)*
Lesions, number	Inflammatory, 15-20 Suppurative, 5 Scarring, 15	Inflammatory, 15-20 Suppurative, 3 Scarring, 15	Inflammatory, 15-20 Suppurative, 4-5 Scarring, 15	Inflammatory, 10-15 Suppurative, 0 Scarring, 15	Inflammatory, 10-15 Suppurative, 0 Scarring, 15
Severity	Moderate	Moderate-mild	Moderate-mild	Mild	Mild
Frequency of recurrences per month	1-2	1-2	1-2	1	1
Blood tests	Normal	Normal	Normal	Normal	Normal
Skindex-29	48.2%	-	40.5%	-	-
Treatment satisfaction	-	-	0	-	-
	6th Infusion (30 Weeks)	*7th Infusion (38 Weeks)*	*8th Infusion (46 Weeks)*	*9th Infusion (54 Weeks)*	*10th Infusion (62 Weeks)*
Lesions	Inflammatory, 10 Suppurative, 0 Scarring, 15	Inflammatory, 10 Suppurative, 0 Scarring, 15	Inflammatory, 10 Suppurative, 0 Scarring, 15	Inflammatory, 10 Suppurative, 0 Scarring, 15	Inflammatory, 10 Suppurative, 0 Scarring, 15
Severity	Mild	Mild	Mild	Mild	Mild
Frequency of recurrences per month	1	1	0-1	0-1	0-1
Blood tests	Normal	Normal	Normal	Normal	Normal
Skindex-29	-	-	-	-	-
Treatment satisfaction	-	-	-	-	-

Table 3. Results for Patient 2

Patient 2	*1st Infusion (0 Weeks)*	*2nd Infusion (2 Weeks)*	*3rd Infusion (6 Weeks)*	*14 Weeks (no treatment)*[a]
Lesions, number	Inflammatory, 55-60 Suppurative, 20-25 Scarring, 10	Inflammatory, 35-40 Suppurative, 4-5 Scarring, 10	Inflammatory, 40 Suppurative, 4-5 Scarring, 10	Inflammatory, 40 Suppurative, 5-10 Scarring, 10
Severity	Severe	Moderate	Moderate	Moderate
Frequency of recurrences per month	1-2	1-2	1-2	1-2
Blood tests	Normal	Normal	ANA, +1/160	Normal
Skindex-29	68.9%	-	69.8%	-
Treatment satisfaction	-	-	0	-

Abbreviation: ANA, antinuclear antibodies.
[a] Last Infusion after 6 Weeks.

Table 4. Results for Patient 3

Patient 3	*1st Infusion (0 Weeks)*	*2nd Infusion (2 Weeks)*	*3rd Infusion (6 Weeks)*	*4th Infusion (14 Weeks)*
Lesions, number	Inflammatory, 20-30 Suppurative, 5 Scarring, 5-10	Inflammatory, 15-20 Suppurative, 3 Scarring, 5-10	Inflammatory, 10-15 Suppurative, 3 Scarring, 5-10	Inflammatory, 10-15 Suppurative, 3 Scarring, 5-10
Severity	Moderate	Mild	Mild	Mild
Frequency of recurrences per month	1-2	1-2	1-2	1-2
Blood tests	Normal	Normal	Normal	Normal
Skindex-29	87%	-	54.3%	-
Treatment satisfaction	-	-	7	-
	5th Infusion (22 Weeks)	*6th Infusion (30 Weeks)*	*7th Infusion (38 Weeks)*	*46 Weeks (no treatment)*[a]
Lesions, number	Inflammatory, 10-15 Suppurative, 3 Scarring, 5-10	Inflammatory, 10-15 Suppurative, 3 Scarring, 5-10	Inflammatory, 10 Suppurative, 1 Scarring, 5-10	Inflammatory, 10 Suppurative, 1 Scarring, 5-10
Severity	Mild	Mild	Mild	Mild
Frequency of recurrences per month	1	1	0-1	0-1
Blood tests	Normal	Normal	Normal	Normal
Skindex-29	-	-	-	-
Treatment satisfaction	-	-	-	-

[a] Last Infusion after 38 Weeks.

improvement because her expectations were higher. The patient occasionally suffered asthenia, headache, dizziness, and nausea after the infusions. The laboratory results were normal.

Patient 2 had more severe disease, with more widespread lesions. An objective improvement in inflammatory lesions and a reduction in the severity of the disease were observed with treatment—but to a lesser extent than with the other 2 patients—and the frequency of recurrences remained unchanged. As shown in Figure 3, the lesions were almost identical before and after treatment. Approximately 2 weeks before the fourth infusion (week 14), the patient suffered a severe recurrence of the disease and, given that she was scheduled for bariatric surgery soon afterwards, it was decided by mutual agreement to discontinue treatment. The subjective outcomes got worse—thus, quality-of-life

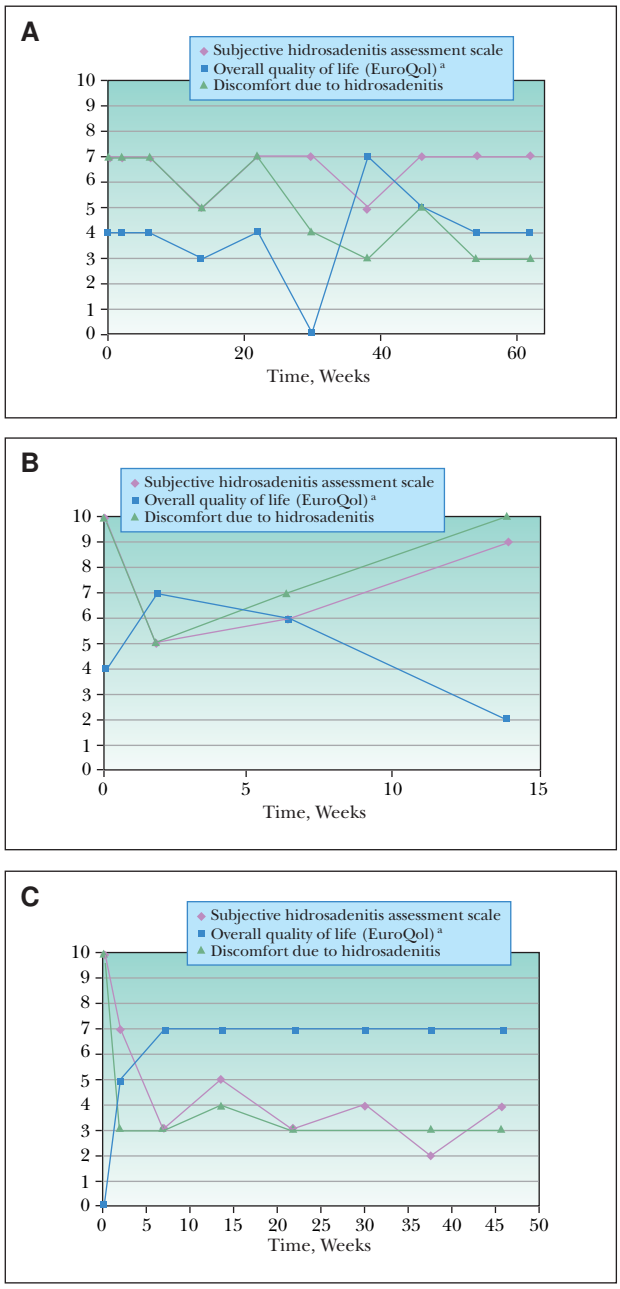

Figure 1. Subjective assessment criteria for hidradenitis suppurativa. A: Patient 1; B: Patient 2; C: Patient 3. [a] Scale proportionally reduced to 0-10 because the original EuroQol scale is from 0-100.

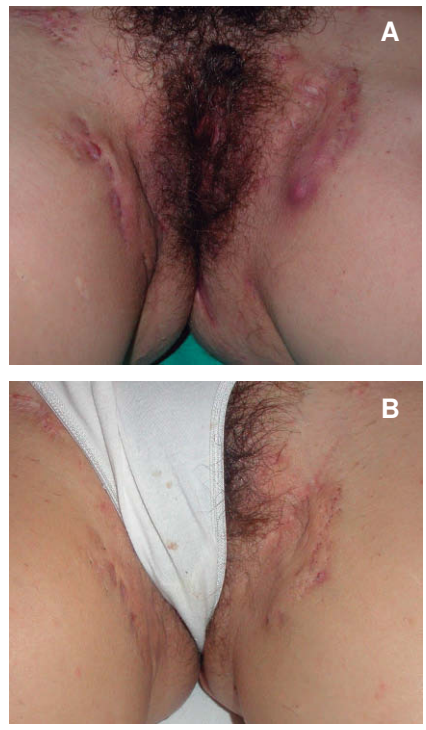

Figure 2. Patient 1. A. Baseline. Lesions in the form of highly inflamed abscesses and nodules that were painful to touch and with occasional fistulous tracts on both sides of the groin. B. After treatment with infliximab for 54 Weeks. Lesions were almost residual, without inflammation, and not suppurative or painful to touch.

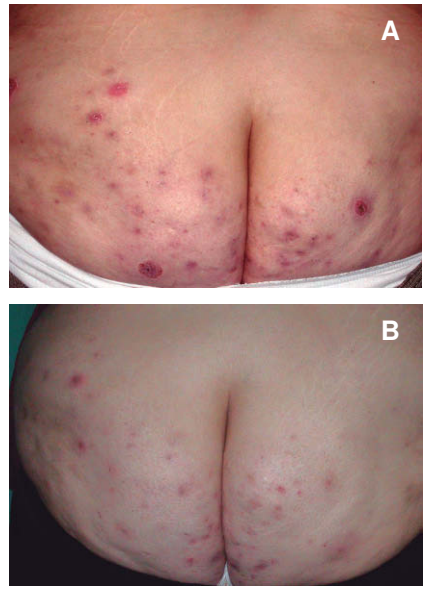

Figure 3. Patient 2. A. Baseline. Erythematous nodular inflammatory lesions disseminated over both buttocks. B. After 14 Weeks of treatment with infliximab. Similar appearance of the lesions, which retain the inflammatory component.

scores and disease assessment and treatment satisfaction scores all decreased. Previous migraine and asthenia also worsened during treatment. In an isolated laboratory test during the third infusion, an ANA titer of 1/160 was documented but this value then returned to normal. Other parameters were normal.

After the first infusion, patient 3 improved with treatment in terms of the number of inflammatory and suppurative lesions, disease severity, and frequency of recurrences. This patient thought that she had improved notably, as reflected by the subjective hidradenitis assessment, and discomfort due to hidradenitis scores and the quality-of-life scales (Skindex-29, EuroQol). Overall, the patient was therefore very satisfied with the treatment. During the treatment period, she reported occasional asthenia and headaches but, after the seventh infusion, she experienced generalized

arthralgia, affecting mainly the ankles, knees, wrists, and fingers. She was referred to the rheumatology service and it was decided to suspend treatment until a possible relationship with infliximab infusions had been ruled out. The results of her laboratory tests were normal throughout the treatment period.

Discussion

Infliximab is a chimeric monoclonal immunoglobulin G1 antibody with a high affinity for TNF-α, a property which enables it to inhibit the proinflammatory action of this protein. Infliximab is currently approved for treating Crohn disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, and ulcerative colitis, but its efficacy has also been demonstrated in other diseases such as graft versus host disease, Behçet disease, sarcoidosis, pyoderma gangrenosum, and hidradenitis suppurativa. On reviewing the literature, we were able to find as many as 8 reports of patients with hidradenitis suppurativa treated with infliximab.[6-13] The largest series was published by Sullivan et al[8] in 2003 and included 5 patients. The other publications were case reports of individual patients. In general, the response to treatment was very good in the articles published. Unlike those reports, we found that the response to infliximab is not always that good in patients with hidradenitis suppurativa. In those reports, however, infliximab happened to be combined with other treatments or follow-up was short, and that may explain the better outcomes in comparison with our results. We found that, in many of the publications, other immunosuppressants such as azathioprine,[10-12] systemic corticosteroids,[8,11] cyclosporine,[8] methotrexate,[13] or even oral contraceptives[8] or rifampicin[13] were added. Our 3 patients did not receive combined therapy—only infliximab—and the outcomes in our patients were variable. It is also worth highlighting that a total of 4 patients of the 11 studied in those publications presented an association between hidradenitis suppurativa and Crohn disease. Patients with Crohn disease are known to respond well to infliximab. Therefore, the good response reported in the literature could be because the lesions that improved spectacularly might in fact have been lesions associated with Crohn disease. No association between hidradenitis and Crohn disease was reported in any of our 3 patients.

In addition, the follow-up period in the cases published varied greatly—from 3 weeks to 2 years. A short follow-up would not provide information on long-term response. In our series, follow-up lasted up to 1 year, and we observed a moderate treatment response in patients 1 and 3.

Finally, the only adverse effect reported in the literature was generalized erythematous rash accompanied by dyspnea after the second infusion of infliximab in a case published by Martínez et al.[12] A new recurrence of the disease during treatment was reported in 3 of the 5 patients in the series published by Sullivan et al.[8] In our study, only 1 of the patients (patient 3) suffered a side effect—generalized arthralgia—that required treatment discontinuation. The other 2 patients only experienced mild drug reactions (dizziness, nausea, asthenia, and headache). We also observed a new recurrence of the disease in patient 2, 15 days after the fourth infusion of infliximab.

In addition to the publications on infliximab therapy,[8,14,15] further support for the suggestion that TNF-α is implicated in the pathogenesis of hidradenitis suppurativa comes from the study published by Cusack et al[16] in which 6 patients with hidradenitis suppurativa were satisfactorily treated with etanercept at a dose of 25 mg twice a week.

In conclusion, we can affirm that infliximab is a moderately useful treatment in some patients. The optimal regimen may not yet have been determined, and so further studies would be justified.

Conflicts of Interest
The authors declare no conflicts of interest.

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