

Long-term efficacy of a single course of infliximab in hidradenitis suppurativa

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Summary

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Key words

acne ectopica, acne skin score, anti-TNF- α , hidradenitis suppurativa, infliximab

Conflicts of interest

None declared.

Background Hidradenitis suppurativa is a chronic inflammatory skin disease characterized by abscess formation, predominantly in the axillae and groins. The disease is difficult to treat and has a severe impact on quality of life. Recently, several case reports have been published describing successful treatment of hidradenitis suppurativa with infliximab and other tumour necrosis factor α inhibitors.

Objectives To evaluate the long-term efficacy of a single course of infliximab.

Methods Ten patients with severe, recalcitrant hidradenitis were treated with infliximab (three infusions of 5 mg kg⁻¹ at weeks 0, 2 and 6) and followed up for at least 1 year. The disease activity was measured using laboratory parameters and a recently developed acne score. The patients rated the efficacy of infliximab on a 10-point scale at regular intervals. Quality of life was measured before and after treatment using the Dermatology Quality of Life Index (DQLI).

Results All patients improved within 2–6 weeks. The average acne score diminished from 164 \pm 50 (mean \pm SD) before treatment to 89 \pm 49 after 1 year ($P = 0.002$). The mean CRP (C-reactive protein) was reduced from 31.7 mg mL⁻¹ to 5.5 mg mL⁻¹ after 1 month ($P = 0.015$). Patients judged the efficacy with a score of 7.9. The mean DQLI was reduced from 18.4 \pm 7.9 before treatment to 9.3 \pm 9.1 after 1 year ($P = 0.007$). In three patients long-lasting improvement was observed, with no recurrence of lesions in a 2-year follow-up period. The other patients showed recurrence of lesions after 8.5 months (range 4.3–13.4 months).

Conclusions Infliximab is an effective treatment in severe hidradenitis suppurativa, leading to reduction of symptoms for a prolonged period.

Hidradenitis suppurativa (acne ectopica/inversa) is a skin disease characterized by chronic purulent inflammation of occluded hair follicles and sebaceous glands, leading to abscesses, nodules, cysts, scars and fistulas. The name hidradenitis is actually a misnomer.¹ Some authors suggest that acne ectopica or acne inversa would be more appropriate terms, but in the international nomenclature the term hidradenitis is preferred. One of the reasons is to distinguish the entity from ordinary acne.² In the majority of patients the lesions are localized in the axillary and inguinal region, but other parts of the body can be affected. It is a disease with a variable clinical presentation.¹ Some patients have only a few nodules or pustules, while others have deep and chronically inflamed sinuses, abscesses and cysts. In its severe form it can be a devastating disease with a great impact on the quality of life.³

The current treatment of hidradenitis suppurativa consists of topical antibacterial or antiseptic lotions, systemic antimicrobials, retinoids, systemic and intralesional steroids, hormonal

therapy, and a wide range of surgical interventions.⁴ Some patients respond well to long-term treatment with tetracyclines (doxycycline, minocycline).⁵ Besides their antibacterial properties, tetracyclines have an anti-inflammatory effect that is not fully understood. An interesting and recent hypothesis is that tetracyclines may inhibit tumour necrosis factor (TNF)- α . TNF- α is produced intracellularly as pro-TNF- α , which is converted into TNF- α by TACE (TNF- α converting enzyme). This enzyme is a metalloproteinase, and metalloproteinases are inhibited by doxycycline.⁶ The possible anti-inflammatory properties of doxycycline in rheumatoid disorders are currently under investigation.⁷

TNF- α is an important pro-inflammatory cytokine, involved in many inflammatory processes, especially the subtype where a neutrophilic infiltrate is present. Blocking TNF- α may improve several dermatological conditions such as psoriasis, pyoderma gangrenosum, Behçet disease, vasculitis, Kawasaki disease, systemic lupus erythematosus, pustulosis

palmoplantar, SAPHO syndrome, reversal reactions in leprosy, subcorneal pustular dermatosis, and hidradenitis suppurativa.⁸

The beneficial effect of infliximab in hidradenitis suppurativa was first observed in patients with Crohn's disease and associated hidradenitis.^{9–11} Subsequently, several patients with hidradenitis suppurativa without inflammatory bowel disease were treated. Between 2003 and 2006 five case reports were published describing in total only nine patients, but with good clinical results.^{12–16} Also the first case reports describing the positive results of etanercept (Enbrel[®], Wyeth, Hoofddorp, The Netherlands) and adalimumab (Humira[®], Abbott, Hoofddorp, The Netherlands) in hidradenitis suppurativa have been published.^{17–19}

In this study, the long-term efficacy of a single course (three intravenous infusions at weeks 0, 2 and 6) of infliximab was investigated in 10 patients with severe hidradenitis suppurativa. The patients were followed for at least 1 year.

Patients and methods

Eleven patients were included in the study between 2004 and 2005, 10 patients completed the study. Patients had to have severe hidradenitis suppurativa, unresponsive to standard treatment as defined above, and with a duration of at least 2 years. Severe hidradenitis suppurativa was defined as having at least five pus-producing lesions and an acne severity score > 100. Obesity (> 100 kg or body mass index > 27) was an exclusion criterion. Patients had to sign an informed consent form because infliximab is not registered for this indication. All patients were screened for tuberculosis by means of chest X-ray and purified protein derivative test (Mantoux).

The severity of the disease before and after treatment was evaluated using a scoring system as described by Sartorius et al.²⁰ For this acne skin score the number of affected regions are counted and the different types of lesions are scored for each anatomical region (Table 1). In addition the

Table 1 Detail of a case record form, illustrating the basic principles of the acne ectopica skin score (adapted from Sartorius et al.²⁰)

Right axilla (3 points)			
Type of lesion	Number	Score	Score
Nodule		× 2	
Fistula		× 4	
Scar		× 1	
Pustule(s)	Yes/no	Yes = 1	
Comedo(s)	Yes/no	Yes = 1	
Sebaceous cyst(s)	Yes/no	Yes = 1	
Size of area:	< 5 cm	2	
	< 10 cm	4	
	> 10 cm	8	
			+3
(no lesions: 0 point)	Total score:		

patients were interviewed at regular intervals and asked to give an overall estimate of the effectiveness of infliximab after 1 month and after 1 year. Quality of life measurements were performed before treatment and after 1 year using the DQLI (Dermatology Quality of Life Index).^{21,22} The clinical efficacy was further documented by means of clinical photography and objective parameters such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and leucocyte count.

Results

Ten patients (six females, four males, average age 41 years, average disease duration 18.5 years, average skin score 164) completed the study. The patient characteristics are summarized in Table 2. All patients improved within 2–6 weeks after the initiation of treatment, although the extent and duration of the effect was quite variable. The inflammatory component was reduced considerably (Fig. 1). The average skin score was 164 ± 50 (mean \pm SD) before treatment and diminished to 108 ± 38 1 month after the third infusion ($P < 0.001$). After 1 year, the average score was 89 ± 49 ($P = 0.002$), but the differences between patients were large. Six patients had improved but in four patients the disease started to recur. In two patients the skin score after 1 year was only slightly lower than before treatment. The individual curves are shown in Figure 2.

Laboratory values

The laboratory values improved in a similar pattern (see Fig. 3). The mean ESR was reduced from 31.8 before treatment to 11.5 1 month after the third infusion ($P = 0.02$). After 1 year the mean ESR was 14.5 ($P = 0.053$). The CRP was reduced from 31.7 mg mL^{-1} to 5.5 mg mL^{-1} after 1 month ($P = 0.015$), and 8.9 mg mL^{-1} after 1 year ($P = 0.03$). The leucocyte count was $10.7 \times 10^9 \text{ L}^{-1}$ before treatment, $8.5 \times 10^9 \text{ L}^{-1}$ after 1 month ($P = 0.03$) and $8.9 \times 10^9 \text{ L}^{-1}$ after 1 year (n.s.).

Patient evaluation

The patients noted improvement from the reduction of pain and discharge, the reduction of the number of dressings needed to cover their lesions, and the ability to resume their normal daily activities such as working or bicycling. The patients rated the efficacy of infliximab on a 10-point scale. One month after treatment the mean patient evaluation score was 7.5, and after 1 year the mean score was 7.9.

The quality of life was measured using the DQLI, a validated score with a maximum of 30 points, which correlates with a severe impact on quality of life. As could be expected, the quality of life before treatment was not good (mean score 18.4 ± 7.9). After 1 year, the mean DQLI improved to 9.3 ± 9.1 ($P = 0.007$).

Table 2 Summary of patient characteristics

Patient no.	M/F	Age (years)	Smoker	Duration (years)	Acne score	DQLI before	DQLI after	Patient score		Remission (months)
								1 month	1 year	
1	F	45	Yes	12	126	10	1	9	10	13.4
2	M	42	Yes	23	126	8	0	9	5	4.3
3	M	43	Yes	15	120	10	2	10	10	26.3 ^a
4	M	46	Yes	18	222	16	12	8	6	7.4
5	F	25	Yes	12	136	12	7	1	9	25.8 ^a
6	F	23	Yes	15	159	24	16	8	8	7.8
7	F	37	Yes	17	125	25	24	6	6	9.9
8	F	53	Yes	26	191	27	7	7	6	7.6
9	M	49	Yes	30	167	24	23	8	9	8.7
10	F	45	Yes	20	270	28	1	9	10	16.4 ^a
Average		41		18.5	164	18.4	9.3	7.5	7.9	12.8

^aNo recurrence yet.

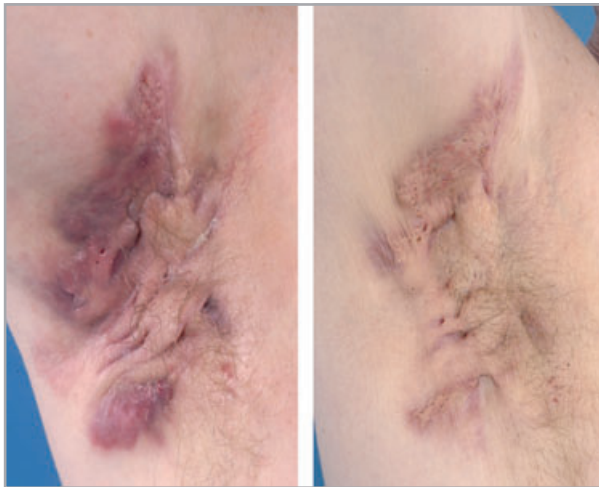


Fig 1. Improvement of hidradenitis suppurativa lesions in the axilla after two infliximab treatments (5 mg kg⁻¹ at week 0 and 2).

Time until recurrence

In three patients a single course (three infusions) of infliximab induced a long-lasting improvement, with no recurrence of lesions in a 2-year follow-up period. The other seven patients showed a recurrence of lesions after a variable time interval. Excluding the three patients who are still in remission to date, the average time until recurrence of lesions was 8.5 months (range 4.3–13.4 months).

Side-effects

Side-effects were observed in three patients. One patient complained of painful sensations and numbness in both legs starting within 2 weeks after the first infusion. Because neurological disorders have been reported as an adverse event of infliximab, it was decided not to continue treatment. This patient was lost to follow-up and was not included in the results of the study. A second patient, who responded well to

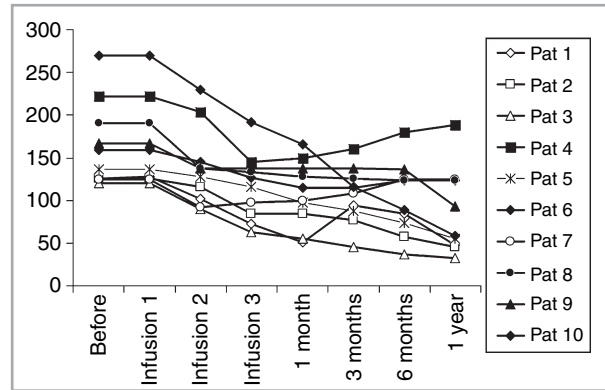


Fig 2. Acne ectopica skin score during treatment and 1-year follow-up.

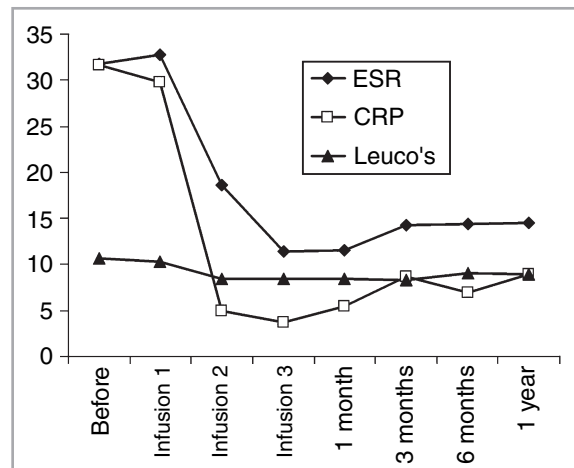


Fig 3. Improvement of the mean erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and leucocyte count during treatment and 1-year follow-up.

infliximab treatment but showed a relapse after 7 months, was treated again with infliximab in her own regional hospital, 8 months after the last infusion. She developed an acute

anaphylactic shock during the first infusion and treatment had to be discontinued. She was subsequently treated with etanercept (Enbrel), but this treatment was discontinued after 4 months because of insufficient improvement. The third patient developed myalgia and fever as a symptom of serum sickness, probably caused by formation of antibodies to infliximab. Initial treatment with a combination of tramadol, paracetamol and ibuprofen, all at maximum doses, did not result in reduction of pain. Treatment with 40 mg prednisone was started, which immediately relieved all symptoms and reduced the fever. The prednisone was gradually reduced over a 6-week period; symptoms did not recur. In the other patients, no side-effects occurred. There were also no infectious complications such as fever, sepsis, or deterioration of skin lesions.

Discussion

This study confirms the efficacy of infliximab in hidradenitis suppurativa that was reported in other case series. All patients improved during treatment. The overall patient judgement was good to very good. Some patients described the infliximab period as the best months they had had in years. The quality of life improved significantly. Objective evaluations like laboratory parameters and the acne skin score confirmed these subjective results. As recommended by Sartorius *et al.*,²⁰ a scoring system specially designed for hidradenitis suppurativa was used in this study. This acne skin score seems to be suitable for monitoring the effect of treatment. There is a good correlation between skin score and laboratory values and the patient's perception of disease activity. Although the acne skin score is probably too time-consuming to incorporate it in daily practice, it is advisable to use this acne score or a similar system for research purposes or to decide whether a patient has severe enough acne to consider treatment with TNF- α inhibitors.

Smoking appears to be an important risk factor for hidradenitis suppurativa.²³ All patients in this study smoked or had been smoking in the past. A high frequency of tobacco use is also reported in other studies describing more severe cases. Kagan *et al.* reported tobacco use in 93% in men and 73% in women treated with surgery.²⁴ In the past, this observation was less obvious because a large part of the population smoked. Nowadays, in the Netherlands only 20–30% of the population is smoking compared with 80–100% of the hidradenitis suppurativa patients. Probably cigarette smoke contains comedogenic compounds. This may be tar or dioxins, which are present in cigarette smoke and may cause acne.^{25,26} Although no studies are available that prove that hidradenitis suppurativa improves after stopping with smoking, patients should be advised to stop.

Some patients responded better to infliximab than others. The best response, as could be expected, was seen in the patients who had a severe inflammatory component around their acne lesions. An example of such a patient is shown in Figure 1. Patients with large, partly epithelialized fistulae and cysts responded only temporarily. Pain and discharge from the

fistulae was reduced during treatment, but recurred after a few months.

Two patients showed a long-lasting (no recurrence after 2 years follow-up) improvement after a single course of infliximab. Both patients had multiple nodules and abscesses over their entire body, but no deep fistulae. The shortest effect (recurrence after 4–3 months) was observed in a patient with multiple deep and already epithelialized sinuses and cysts, and a pilonidal sinus that had been treated surgically several times without success.

As the majority of patients showed recurrence of symptoms some months after a single course, the next step would be to offer long-term treatment to the patients who respond well to infliximab. A recent study shows that long-term reduction of symptoms is possible.¹⁶

One of the problems with long-term treatment is the possible development of antibodies against infliximab.²⁷ In patients with psoriasis or rheumatoid arthritis, combination with low-dose methotrexate may inhibit antibody formation. But in hidradenitis suppurativa patients it would be uncommon to prescribe methotrexate, because methotrexate is not an effective treatment option for hidradenitis.²⁵ A question is whether there is sufficient evidence that methotrexate suppresses antibody formation. More recent studies showed that the effect of methotrexate on antibody formation is modest.²⁸

The other problem of long-term treatment is the high cost of infliximab and the other TNF- α inhibitors. Since hidradenitis suppurativa is not a registered indication for infliximab, many health insurances are not willing to finance it. Registration studies should be performed to build up the evidence. However, because the number of patients with severe therapy-resistant hidradenitis is relatively small compared with other indications such as rheumatoid arthritis, psoriasis and inflammatory bowel disease, it is uncertain whether the manufacturers are willing to initiate these studies. In the mean time, incidental off-label use for the most severe cases remains the only option. In the Netherlands, some health insurances take responsibility and reimburse anti-TNF- α treatment in selected individual cases. The acne skin score could become an important tool to select patients who are eligible for this type of expensive treatment. Considering the severity of the disease, with quality of life scores that are much worse than in psoriasis patients who receive anti-TNF- α treatment,^{3,29} this patient group certainly deserves to have available a powerful last-resort treatment option.

Acknowledgments

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