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REVIEW ARTICLE

Treatment of Hidradenitis Suppurativa with Tumour Necrosis Factor-α Inhibitors

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Hidradenitis suppurativa (HS) is a common inflammatory skin disease. Medical treatment is often disappointing and in severe disease surgery remains the therapy of choice. Extensive surgery may be effective but also mutilating. Patients experience a significant reduction in quality of life and the need for new treatment modalities are urgent. In recent years patients with HS have been treated off-label with tumour necrosis factor-α (TNF-α) inhibitors with a varying degrees of effect. We performed a systematic review of papers retrieved from two databases (PubMed and Web of Science) using the following keywords: hidradenitis suppurativa, acne inversa, infliximab, etanercept, and adalimumab. A total of 34 publications were retrieved, describing treatment of 105 patients. Most cases report treatment with infliximab (52/105). A positive treatment outcome was reported in 90/105 cases, with only 7/105 non-responders and 8/105 patients experiencing side-effects. The side-effects were comparable to those seen in other TNF-α inhibitor studies. In the majority of cases the treatment was effective when given as a suppressive therapy, but 15/105 cases were described with long-term remission (≥3 months) after the end of therapy. In most publications follow-up was, however, insufficient to allow a systematic exploration of this. TNF-α inhibitors seem to be effective in the treatment of HS. However, several questions remain to be answered through specific studies. This review has also identified a need for more standardized reporting of the outcomes as well as randomized controlled trials in this disease. ***Key words: hidradenitis suppurativa; tumour necrosis factor-α inhibitors; infliximab; etanercept: adalimumab.***

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Hidradenitis suppurativa (HS) is a common inflammatory skin disease characterized by formation of multiple abscesses and nodules in the apocrine gland-bearing areas (1). Localized primarily in the intertriginous areas, such as the groin, axilla, gluteal cleft and inframammary folds. The point prevalence of HS among young adults is 4.1%, with a female preponderance, and the age at onset is the third decade (2). Aetiology and pathogenesis are unknown, but follicular occlusion appears to play a role. Histology is characterized by chronic inflammation often containing granulomatous changes, sinus tract formation and scarring. Several case series report an association with Crohn's disease (3, 4). Some studies indicate that hormones, obesity, bacterial infections and smoking may play a role in development or aggravation of the disease (5, 6), although the evidence is variable. Patients diagnosed with HS often experience a significant reduction in quality of life due to the location of, and discharge from, the lesions (7, 8).

HS is a difficult condition to treat (9). Currently available therapeutic options include general interventions such as weight loss, cessation of smoking or reduction of shear forces combined with medical and surgical treatment. Only 3 randomized controlled trials of medical treatment have been published and these were all conducted before 1998. Two trials showed improvement of abscesses and pustules, but not of inflammatory nodules during long-term application of topical clindamycin (10, 11). No statistically significant difference in efficacy was found between topical clindamycin and systemic tetracycline administration (11). In a trial published in 1986, 2 types of anti-androgen therapy in women with HS were compared, and it was shown that some patients achieved disease remission after 6 months of treatment (12). In view of the supposed connection between HS and acne, isotretinoin therapy has been repeatedly tried on HS, but with very limited success, while the aromatic retinoids acitretin/etretinate have been reportedly successful in case reports, but do not produce permanent resolutions of the lesions (13–15). Although medical treatment with antibiotics, cyproterone acetate, oral contraceptives, dapsone or cyclosporine is recommended in the early stages of HS, medical treatment is often disappointing. In severe disease wide surgery therefore remains the therapy of choice, as clinically unrecognized, subclinical lesions may otherwise remain (16). Extensive surgery may be effective and reduce the recurrence rate, but can be associated with significant morbidity, especially in the genitofemoral area (17). Quality of life scores in patients with HS appear to be worse than those in comparable psoriasis patients. The

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lack of effective treatment and associated physical and psychological consequences can be devastating for the patients and there is therefore a continued unmet need for new treatments.

In recent years biologic agents (tumour necrosis factor (TNF)-α inhibitors: etanercept, adalimumab and infliximab) have been introduced and efficacy in the treatment of several dermatological diseases has been suggested. TNF-α is an important pro-inflammatory cytokine produced by many different cells, though mainly by macrophages and monocytes. It can be found in the basal layer of epidermis, sweat glands and hair follicles. TNF-α binds to specific receptors and induces an intracellular cascade, which leads to a pro-inflammatory reaction. Targeting TNF-α may block this cascade at a critical point.

The beneficial effect of infliximab in HS was first described as a serendipitous finding in patients with associated Crohn's disease (18). When HS affects the anogenital region it can be difficult to differentiate from the extra-intestinal manifestations of Crohn's disease, because of the overlapping clinical appearance and histology. Differentiation between the two entities is, however, usually possible. In recent years patients with HS without any history of Crohn's disease have therefore been treated off-label with infliximab and other TNF-α inhibitors, with varying degrees of effect. The total number of cases has now reached a point where the potential effects of TNF-α inhibitors in HS may be meaningfully reviewed.

For this purpose we performed a systematic search of the English language databases (PubMed and Web of Science) using the following keywords: hidradenitis suppurativa, acne inversa, infliximab, etanercept, and adalimumab. We retrieved a total of 34 publications. Of these 20 reported on patients treated with infliximab (in total 52 patients); 7 treated with etanercept (in total 37 patients), and 7 treated with adalimumab (in total 16 patients); altogether 105 patients. A systematic review of these cases is presented.

INFLIXIMAB (refs 19–38, Table I)

Infliximab (Remicade®) is a chimeric IgG antibody that binds to the TNF-α molecule, decreasing the effect of the cytokine. It is composed of human-derived constant regions and mouse-derived variable regions and is administered as an intravenous infusion.

Infliximab infusions were given as the standard induction regimen used for psoriasis and fistulating Crohn's disease, and in approximately 50% of the cases it was followed by maintenance treatment every 4–8 weeks. Improvement with infliximab was reported in 45 of 52 patients. Of these 45 patients, 28 showed improvement only during treatment, while 17 had a durable response after cessation of treatment. In 6 case reports no improvements were seen in a total of 7 patients. Of these, 6 patients had a single induction course (week 0, 2, 6) while one received further infusions every 8 weeks (30).

A standard dose of 5 mg/kg was used except for a single case report where 10 mg/kg was given (31). In 8 case reports (24 patients), only the induction regimen was administered (19, 21, 24, 25, 28, 29, 32, 35). A majority of these (13/24) patients had reported improvement for various periods of time up to 2 years after induction treatment. Six patients showed improvement only under treatment (25, 28) and 5 patients reported no improvement (28, 29, 35). One paper chose a different dosage schedule (23). Five patients were given a maximum of 2 infliximab infusions. All patients improved under treatment (evaluations were made only 3–7 days after the last dose).

In 11 papers, a total of 22 patients receiving maintenance treatment were described (20, 26, 28, 29, 30–33, 36–38). In the majority of case reports the maintenance treatment was given throughout the time for follow-up. In 2 reports (4 patients) the treatment was stopped when improvement was obtained and continued effect was reported up to years (33, 36). There was a great variation in the overall duration of treatment, in one case up to 2 years (20) and the intervals between the infusions were between 4 and 8 weeks. In this group of patients, 20/22 had a various degrees of improvement under treatment, and only 2 had no effect.

In some cases concomitant therapy was provided. The information about additional treatment was limited in most studies. Nevertheless, two reports clearly describe monotherapy with infliximab in a total of 13 patients (28, 31). None of the patients had sustained improvement after the treatment was stopped, 11 patients improved under treatment (in 3 patients additional treatment with immunosuppressives was added after 6 months due to declining response to infliximab), and 2 patients had no effect whatsoever.

Looking at a total of 17 patients with reported long-term effect following infliximab (induction or maintenance treatment stopped after improvement was achieved) the information about possible concomitant therapy under and after treatment was limited. Different kinds of immunosuppressives and antibiotics were administered alone or in combination.

An assessment of the influence of possible co-morbidities was attempted in spite of the lack of systematic reporting. Tobacco smoking was reported in only one study (32). Six patients had coexisting Crohn's disease; 50% had improvement after treatment at a minimum of 3 months and 50% improved under treatment. One patient had ulcerative colitis and no signs of relapse until 3.5 months after the end of treatment (24). In 3 reports (27, 28, 34) describing 9 patients without any signs of Crohn's disease, 5 patients had improvement

Table I. *Effect of treatment with infliximab, etanercept and adalimumab in patients with hidradenitis suppurativa*

				Effect duration after end of treatment		
Drug/ref	*n*	No effect	Effect during treatment only	4–12 weeks	13–26 weeks	27–52 weeks
Infliximab (*n*=52)						
Martinez et al. 2001 (19)	1				1	
Katsanos et al. 2002 (20)	1		1 (M) Crohn's[a]			
Roussomoustakaki et al. 2003 (21)	1				1 (F) Crohn's	
Lebwohl & Sapadin 2003 (22)	1		1 (M)			
Sullivan et al. 2003 (23)	5		5 (4 F, 1 M)			
Adams et al. 2003 (24)	1				1 (M)	
Rosi et al. 2005 (25)	1		1 (F) Crohn's			
Maalouf et al. 2006 (26)	1		1 (M)			
Thielen et al. 2006 (27)	1		1 (M)			
Fardet et al. 2007 (28)	7	2 (M)	5 (3 F, 2 M)			
Usmani et al. 2007 (29)	3	2 (1F, 1M)	1 (F)			
Pedraz et al. 2007 (30)	3	1 (F)	2 (F)			
Fernández-Vozmediano & Armario-Hita 2007 (31)	6		6 (4 F, 2 M)[b]			
Mekkes & Bos. 2008 (32)	10				1 (M)	9 (6F, 3M)
Moschella 2007 (33)	3		1 (M)	1 (F) Crohn's	1 (F) Crohn's	
Antonucci et al. 2008 (34)	2	1 (M)	1 (F)			
Pedraz et al. 2008 (35)	1	1 (F)				
Elkjaer et al. 2008 (36)	2			1 (M)		1 (M)
Montes-Romero et al. 2008 (37)	1		1 (M)			
Goertz et al. 2009 (38)	1		1 Crohn's[c]			
Etanercept (*n*=36)						
Jurgensmeyer & Fleisher 2004 (41)	1		1			
Cusack & Buckley 2006 (42)	6		6 (F)			
Henderson 2006 (43)	1			1 (F)		
Giamarellos-Bourboulis et al. 2008 (44)	10			10		
Zangrilli et al. 2008 (45)	1		1 (M)			
Lee et al. 2009 (46)	14	2	12			
Sotiriou et al. 2009 (47)	4		3 (2F, 1M)	1 (F)		
Adalimumab (*n*=16)						
Ravat et al. 2005 (49)	1		1 (M)			
Scheinfeld et al. 2006 (50)	1		1 (M)			
Moul & Korman 2006 (51)	1		1 (M) Crohn's			
Sotiriou et al. 2009 (52)	3		3 (F)			
Yamauchi et al. 2009 (53)	3		3 (F)			
Harde et al. 2009 (54)	1		1 (M)			
Blanco et al. 2009 (5)	6		6 (2 M, 4 F)			

[a]Co-morbidity and main indication for anti-TNF treatment. [b]3 decline in effect over time. [c]after 14 months no effect.
F: female; M: male; Crohn's: Crohn's disease.

under treatment and 2 had no effect at all. No specific information about whether the patients had Crohn's disease was presented in the other reports.

Comments

The majority of patients (28/52) only had effect during treatment, but this might be underestimated, because evaluation was made during treatment or shortly (3–7 days) after the end of treatment. This means that little is known about the potential long-term effect of infliximab after the end of therapy. Lack of initial effect or short time to relapse may be speculated to have led to continued treatment and hence affected the treatment schedule reported. The response to treatment showed great individual differences. It is speculated that this could be due to the dose, the dosing frequency or disease severity as described by the different stages of HS. The difference could also be due to variations in the clinical manifestations of HS. Some patients had only a few nodules or pustules, while others had chronically inflamed sinuses, abscesses and cysts. In several cases the best effect was seen in patients who had a strong inflammatory component. This clearly highlights the importance of utilizing standard criterion and tools to measure disease. Patients with a clear description of large, partially epithelialized fistulae and cysts reported temporary responses.

Infliximab seems to be effective in patients with a dominating inflammatory component. A conclusion about the efficacy in favour of short-term or long-term treatment cannot be made from the available cases, although continuous treatment seems to be required in many patients. Patients with psoriasis and rheumatoid arthritis are often treated with a combination of infliximab and methotrexate to prevent the formation of antibodies against infliximab. Methotrexate has only limited effect in treating HS, therefore studies regarding the

effect and safety of adjuvant therapy with methotrexate need to be conducted (39).

Seven reported patients had to discontinue treatment due to side-effects similar to those reported in other infliximab studies of, for example, psoriasis (18, 19, 26, 28–30). One recent published case reports infectious complication in a patient with fatal pneumococcal sepsis (40).

ETANERCEPT (refs 41–47, Table I)

Etanercept (Enbrel®) is a recombinant completely soluble TNF-α-receptor fusion protein. It consists of two associated dimers each containing identical chains of the TNF-α fused with the Fc portion of human IgG1. Etanercept prevents the effects of TNF-α by competitively binding TNF-α at its receptor.

Etanercept was self-administered as subcutaneous injections. The dosage and frequency of administration varied between 25 and 50 mg once or twice a week. In 3 case reports (5 patients) the initial dose at 25 mg twice weekly was increased to 50 mg twice weekly due to lack of response (41, 42, 47). Two prospective studies initiated treatment with 50 mg once or twice weekly and decreased the dose after 12 or 24 weeks of treatment (45, 46). In most of the cases the effect was monitored during treatment and only short follow-up. Improvement was described in 35/37 patients: 23 patients only had effect during treatment, while 12 patients had continued effect in a period 4–12 weeks after the treatment was discontinued. Two patients did not have any effect after 8 weeks of treatment (46). Etanercept was given as monotherapy (42, 44, 46, 47) or in combination with antibiotic and immunosuppressive. A case report indicated that the combination of systemic antibiotic and etanercept was essential, because the patient had flare-up when either antibiotic or etanercept was withdrawn (43). No major infectious side-effects were reported in the cases listed above. However, one case report described bilateral candida chorioretinitis following etanercept treatment (48).

Comments

Five of 7 published studies uniformly suggest the drug to be useful in the long-term treatment of HS as monotherapy. A recent published prospective study demonstrated minimal evidence of clinically significant efficacy of monotherapy with etanercept in the treatment of HS (46). In this study patients were, however, excluded if they experienced disease flares requiring antibiotic treatment, which was allowed in other reported cases, and the predefined criteria for clinical efficacy were set high (42). The treatment was generally well tolerated in the published cases. Further studies need to be conducted to estimate the effect of etanercept as monotherapy and in particular in combination with antibiotics and immunosuppressives.

ADALIMUMAB (refs 49–54, Table I)

Adalimumab (Humira®) is a fully human monoclonal antibody IgG1 that binds both soluble and membrane-bound TNF. It can be administered at home and is available in an auto-injection pen device. Adalimumab was self-administered as a subcutaneous injection in a dose of 40 mg, except for one case report where the initial dose was 80 mg (54). The frequency of administration was, in the majority of cases, initiated as 40 mg every other week (50–53). In 2 cases (4 patients) the dosage was increased to 40 mg weekly to maintain clinical improvement (50, 53). Improvement under treatment was reported in all patients. In a recent published case report by Sotiriou et al. (52) the treatment was discontinued and evaluation was made after 3 months. At that time all 3 patients had relapses, but to a less severe extent than pre-treatment. Two patients had been treated successfully with infliximab for several months, but were switched to adalimumab due to waning efficacy. Both patients had clinical improvement. No severe side-effects were reported. The beneficial effect of adalimumab treatment in refractory HS has been reported in 6 patients undergoing standard dose therapy for one year (55). In 2 patients, the adalimumab dosage could be reduced to 40 mg every third week.

Comments

Being the most recently introduced TNF-α inhibitor few data are available on adalimumab. The reported cases indicate clinical response when adalimumab is administered continuously. No side-effects were reported up to the maximum follow-up of one year. Further studies need to be conducted to determine the correct dose and frequency of administration.

CONCLUSION

In recent years the use of biological therapy has been introduced to the field of dermatology and advocated for the treatment of several inflammatory conditions such as psoriasis, pyoderma gangrenosum, and toxic epidermal necrolysis. The aetiology of HS is not known, but it has been speculated that both dysregulation of the inflammatory cascade in the hair follicle as well as wound healing may play a role (56, 57). The anti-inflammatory effects of TNF-α inhibition are well known, and studies have suggested that the use of TNF-α may also play a role in wound healing and chronic wounds (58, 59). TNF-α inhibition may therefore affect several pathogenic mechanisms in HS.

This systematic review of the published cases of TNF-α inhibition in HS suggests that only a minority of patients do not experience effect (7/105), while the incidence of side-effects is comparable to that seen in other case series with this class of drug (8/105). It would appear that, analogous to the situation in psoriasis, the majority of patients have effect during treatment, but encouraging reports exist of long-term remission of HS induced in particular following the use of infliximab and adalimumab. TNF-α inhibitors therefore seem to have a considerable potential in the treatment of HS, even taking into account the positive publication bias induced by using a new class of drugs to obtain a good result in a difficult-to-treat dermatosis, However, several questions remain to be answered. In addition to the exact definition of the role of TNF-α in this disease, the effect of individual, dose-dependent and drug-dependent variables remain undescribed. This is primarily due to the lack of standardized methods to describe the protean manifestations of HS, and varying treatment regimens reported (60, 61). Although encouraging, the present literature has also identified a strong need for more standardized reporting of the outcomes as well as randomized controlled trials in this most distressing disease. Recent observations regarding the levels of TNF-α in patients with HS, however, suggest that this may be a very worthwhile pursuit (62).

Conflict of interest: RL has been an investigator in clinical studies for Wyeth; and GJ has received honoraria for advice given to Centocor and Abbott, is on the advisory board of Schering-Plough, Wyeth and Abbott in Denmark, and has acted as investigator for Schering-Plough, Abbott and Wyeth.

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