Treatment of Hidradenitis Suppurativa with Tumour Necrosis Factor-alpha Inhibitors: An Update on Infliximab

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Accepted June 4, 2010.

In the November issue of *Acta Dermato-Venereologica*, Haslund et al. (1) performed a systematic search using hidradenitis suppurativa (HS), acne inversa, infliximab, etanercept and adalimumab as key words. A total of 20 articles regarding the use of infliximab in HS (52 patients in total) were retrieved and evaluated for a systematic review. The effort put into reviewing all the literature is highly appreciated, but in addition herein we would like to integrate new information regarding another 42 patients, seven of these from our personal experience, evaluating other selected variables that will add new insights to the work of Haslund et al. (1–5, 11).

METHODS

A PubMed search (using the key words: hidradenitis suppurativa, acne inversa and infliximab) was performed. We found 23 publications, regarding 95 patients treated with infliximab for HS published between the years 2001 and 2010 (1–11). We were not able to retrieve one case report (4), but data regarding safety of this patient were analysed.

Ninety-four patients were evaluated for the following variables: sex, number of areas involved, severity, smoke habits, associated co-morbidities, number of infusions, mean time of treatment, associated therapy, response during treatment, type of treatment (induction or continuous), mean follow-up time and outcome (Table SI (http://adv.medicaljournals.se/article/abstract/10.2340.00015555-0989)). Associated co-morbidities are shown in Table SII (http://adv.medicaljournals.se/article/abstract/10.2340.00015555-0989).

RESULTS

Regarding efficacy, in 61 patients treated until 2009, 85.3% (52 patients) obtained a moderate or marked improvement during treatment, eight patients (13.1%) obtained a scarce or absent improvement, and in one case data were not available. A recent randomized placebo controlled trial (5), with 33 patients who received infliximab and 18 who received placebo, demonstrated the superiority of infliximab vs. placebo after 8 weeks of treatment. Unfortunately, data regarding long-term follow-up (52 weeks) were collected in only five patients with two sustained improvements and three relapses after 22 weeks of infliximab (5).

Regarding treatment schedules, 44 patients (46.8%) followed only an induction treatment with four or less infusions, 48 patients (51.1%) followed continuous therapy after the induction phase (day-0, week-2 and week-6), and in two patients treatment schedule was not available. The mean number of infusions administered was 4.9 (data available only in 66 patients) and the mean duration of treatment was 24.6 weeks (data available only in 67 patients). Mean follow-up time was 53.8 weeks (assessed in 48 patients) and outcome evaluation at the end of follow-up was assessed in 66 patients: seven patients (10.6%) had stable response after withdrawal of infliximab, four (6.1%) were stable while on therapy, 15 patients (22.7%) recurred after suspension (mean time to recur of 28.2 weeks), in 8 patients (12.1%) a loss of response during continuous treatment was reported. Twenty-one patients (22.1%) suspended therapy due to severe adverse events (SAE), in eight patients (8.5%) there was no response and in 31 patients (32.9%) data regarding outcome at the end of follow-up were not available. Infliximab monotherapy was administered in 61 patients (64.9%). Regarding combination therapy, 13 patients (13.8%) received immunomodulators (methotrexate: 9 patients), four patients received antibiotic therapy and data were not available for 16 patients. Infliximab monotherapy was suspended and re-introduced because of recurrence of HS in six patients with good response in four patients with SAE and withdrawal in two patients. Ninety-five patients were evaluated for safety (Table I). Seventeen patients experienced adverse events probably related to the immunogenicity properties of infliximab. Comparing the frequency of immunogenicity-related SAE between the group of combined infliximab and immunomodulators (one event in 17 patients) with the rest of the patients treated with infliximab that we presumed treated in monotherapy (16 events in 78 patients), the rate of immunogenic adverse events is 1:3.5.

Table I. *Number of severe adverse events that required suspension of infliximab therapy (95 patients evaluated)*

Severe adverse event	% (ref)
Infusion reactions ($n=8$)	8.4 (2, 3, 5, 10, 11)
Cancer diagnosis ($n=2$)	2.1 (1, 5)
Peripheral neuropathy ($n=2$)	2.1 (1, 5)
Lupus reaction ($n=1$)	1.1 (3)
Generalized swelling, itching and erythema ($n=1$)	1.1 (9)
Generalized arthralgia ($n=1$)	1.1 (6)
Anaphylactic shock after re-introduction ($n=1$)	1.1 (1)
Serum sickness ($n=1$)	1.1 (1)
Fatal pneumococcal sepsis ($n=1$)	1.1 (4)
Pregnancy ($n=1$)	1.1 (11)
Hypertension ($n=1$)	1.1 (11)
Presumed tuberculosis ($n=1$)	1.1 (1)
Total ($n=21$)	22.1

DISCUSSION

We can conclude that infliximab is effective in severe cases of HS where other conventional available therapies have failed. However, many concerns arise when we look at the long-term data available. In the group of patients treated continuously (24 patients) a loss of efficacy was seen in 33% (8 patients) and in patients treated intermittently (withdrawal and re-introduction) a high incidence of SAE (33%) was seen. We interpreted this data as following: infliximab is a good tool, but not the ultimate alternative; sequential surgical therapy might improve long-term results. Re-treatment should be considered as a high-risk intervention that can be avoided by switching to other anti-TNF-α agents that have already proved their efficacy in HS (1). Immunogenicity has been implicated in loss of infliximab's efficacy in patients treated for other chronic inflammatory diseases and can be a possible explanation of our findings (12, 13). The second main concern regards the safety profile. A high rate of SAE (22.1%) was detected, with a significant difference between the infliximab-monotherapy vs. infliximab-immunomodulator group. This led us to suggest that immunomodulatory therapy, mainly methotrexate, should be used concomitantly with infliximab, even if methotrexate has no proven efficacy in HS (14), just to prevent immunogenicity and autoimmunity SAE (12, 13).

Contrary to Haslund et al. (1) we think that a clear conclusion regarding the efficacy of infliximab in HS can be drawn, because improvement was obtained in 85% of cases (52 of 61 patients), data recently confirmed by Grant et al. (5) in a randomized prospective placebo-controlled trial. Regarding the long-term efficacy, loss of response and schedule treatment (induction vs. continuative) are the two biggest determinants for outcome; perhaps we should not expect a complete and sustained remission of HS with few infliximab infusions as we do not expect it in other chronic inflammatory conditions. Our analysis of concomitant treatment and co-morbidities differs from comments reported by Haslund et al. We found that 21 patients (22.1%) discontinued therapy due to SAE in contrast with the seven patients (13.5%) reported by Haslund et al; a higher percentage compared with SAE reported in other infliximab studies (15).

In accordance with Haslund et al. (1) we agree that large controlled studies with long-term follow-ups, regarding the use of infliximab (ideally associated with an immunomodulator such as methotrexate) in severe HS are needed not only to standardize our way of using the drug, but mainly for helping patients to obtain health insurance reimbursements considering that infliximab does not have a registered indication for HS.

The authors declare no conflicts of interest.

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