Anti-Tumour Necrosis Factor-alpha Therapy in Crohn's Disease: Clinical and Health Economic Aspects

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ABSTRACT

Objectives: Crohn's disease is a chronic, relapsing inflammatory disease of the gastro-intestinal tract. Tumour necrosis factor-alpha (TNF-α) is a pro-inflammatory protein that is believed to play a major role in the pathogenesis of Crohn's disease (CD). Infliximab, a chimeric anti-TNF-α proclonal antibody, which inhibits the bioactivity of TNF-α, is a recent and exciting strategy in the treatment of CD. The purpose of this study was twofold. Firstly, the economic impact of infliximab therapy was examined. Secondly, chronic active Crohn's disease patients were analysed for their response to infliximab therapy. **Patients and Methods:** The medical records of 25 patients from the Department of Gastroenterology, AMNCH (Dublin) were analysed. Health-care utilization data were collected for each patient over the two years pre- and post-infliximab therapy. The medical records of all chronic active patients were analysed to investigate the role of infliximab as a steroid-sparing agent. The CDAI (Crohn's Disease Activity Index) was employed as a reference for evaluating disease activity. **Results:** Following initiation of therapy with infliximab, the total number of hospital admissions decreased by 46.9%. The mean duration of hospital stays remained unchanged. The mean daily dosages of prednisolone decreased over the 12 months post-infliximab therapy, compared with the 12 months prior to therapy. Similarly, the mean daily dosage of budesonide decreased in the 12-month period following initiation of infliximab therapy. **Conclusion:** The findings from this study of 25 patients with chronic active CD are comparable to those previously achieved in the controlled setting of clinical trials. In addition, this study demonstrated that infliximab may reduce the overall costs of management of Crohn's disease by limiting associated health care utilization. Results also supported the theory that infliximab acts as a steroid-sparing agent. Further investigation into the impact of infliximab on healthcare usage and the prescription of corticosteroids could be an exciting and challenging field for research in the future.

INTRODUCTION

Crohn's disease is a chronic, relapsing, inflammatory disease of the gastro-intestinal tract. Manifestations of the disease may be severe, and lead to long-term therapy with a variety of medications and/or surgery. There are two main classifications of the disease, including the relapsing-remitting chronic active variety, and the penetrating or fistulising variety. Tumour necrosis factor-alpha (TNF-α) is a pro-inflammatory protein believed to play a major role in the pathogenesis of Crohn's disease (CD). Significantly higher levels of TNF-α have been found in the intestinal mucosa of patients with CD compared with controls. The development of an anti-TNF-α antibody, which inhibits the bioactivity of TNF-α, is a recent and exciting strategy in the treatment of CD.[1] Infliximab, a murine-human chimeric anti-TNF-α proclonal antibody, is one such pharmacological agent. In clinical trials, approximately two-thirds of patients with chronic active CD responded to this therapy, and one-third of patients remained in full clinical remission in the short-term. However, it may not be possible to accurately identify potential responders and non-responders.

Although CD is a severe, debilitating condition, the life expectancy is the same as for the general population.[2] Thus, many patients with CD will require treatment for most of their adult lives. A study performed by Cohen and colleagues elucidated that surgery accounts for the majority of hospitalisations in Crohn's disease, almost 40% of the total cost, and 75% overall charges and reimbursements.[3] Due to the initial high cost of treatment, determining which sub-groups of patients will respond to specific cytokine therapy has important implications for patient management and remains the challenge of the future.

It has been claimed that infliximab (Remicade®, Centocor, Inc., Malvern, PA, USA) has a role as a steroid-sparing agent in luminal Crohn's disease.[4] However, confirmation in clinical settings has proven difficult. A recent study evaluated the impact of infliximab on steroid usage using as "steroid equivalence test," but failed to yield statistically significant results.[5]

MATERIALS AND METHODS

Patients

The Department of Gastroenterology, AMNCH, has treated 46 patients with infliximab over a two and a half-year period, 25 of which were investigated for this study. This group of 46 patients represents the largest single experience with this treatment in Europe outside clinical trials. In 1998, prospective documentation of clinical response, health economic and quality of life data, and blood for serum cytokine analysis was initiated. Patient records were analysed for determination of the health economic impact of treatment, and for investigation of the role of infliximab as a "steroid-sparing" agent. These patients included both males and females, and those experiencing both chronic active and fistulising forms of CD.

Disease Activity

The CDAI (Crohn's Disease Activity Index) is a standard measure of the activity of disease and this proved a useful tool in this study. A score of higher than 150 indicates active disease. Response to infliximab was defined as a reduction in the CDAI either by 70 points or more, or to a score of less than 150.

The Economic Impact of Infliximab

The determination of economic data involved intensive perusal of each patient's medical records. All healthcare usage was recorded for each patient for two years pre- and post-infliximab therapy, and this period of time was divided into eight six-month intervals. For each patient, detailed economic analysis was performed, recording: a) hospital admissions, b) length of stay, c) visits to the A & E department, d) the number of gastrointestinal (GI) surgeries performed, e) the number of courses of IV steroids administered to each patient, f) the number of occasions where TPN was required, and if so, the duration of TPN in days, g) the number of OGDs, or colonoscopies performed, as well as other procedures that involved endoscopy such as ERCP, h) the number of GI x-rays, ultrasounds and CTs etc. performed, i) the number of other (non-GI) procedures performed including other surgical procedures, j) the number of non-GI x-rays, ultrasounds and CTs etc. performed, k) the number of GI clinic visits and l) the number of non-GI clinic visits. This was collated with existing prospective data. The methodology also involved visiting or contacting a number of other hospitals to collect information.

Infliximab's Role as a Steroid-Sparing Agent

In this study, the medical records of all chronic active patients were analysed, noting the dosages and duration of treatments with standard systemic oral steroids (e.g. prednisolone) and the more locally acting, gastrointestinal tract-specific steroids (e.g. budesonide). The years leading up to and following initiation of treatment with infliximab were analysed, and an average daily dosage of both prednisolone and budesonide was calculated for each 6-month period. Finally, the weeks in which prednisolone was not administered were calculated, again in each 6-month period pre- and post-infliximab therapy.

RESULTS

A total of 25 patients were analysed for age, gender, CDAI, sub-type of CD, length of follow-up, smoking status, and response to infliximab (Table 1). There was a 73.1% response to infliximab.

Analysis of Economic Data

Analysis of the economic data yielded interesting results. Table 2 summarises the main components of health-care usage as noted from each patient's medical records. The total usage of health-care facilities was calculated for the period before and after first infusion of infliximab, and the results were compared, with a percentage increase or decrease being noted.

Certain parameters, however, underwent little change. For example, although the number of admissions to hospital decreased

Table 1. Patient Characteristics

Characteristic	
Age, mean ± std. error	34 ± 2.04 years
Gender	73% female
CDAI, mean ± std. error	268.0 ± 24.08
Predominant CD sub-type	69% chronic active
Follow-up, mean ± std. error	20.2 ± 1.64 months
Smokers/ex-smokers	31%/12%
Response to infliximab	73% response

CDAI, Crohn's Disease Activity Index

Table 2. Economic Data

Type of Healthcare Use	Pre-Infliximab	Post-Infliximab	% Increase or Decrease
Hospital admissions (total n)	32	17	47% decrease
Admissions during which IV steroids were employed(%)	43.5%	19.2%	24% decrease
Patients requiring at least one endoscopy (%)	63.5%	27.3%	36% decrease
Patients requiring at least one radiological procedure (%)	63.5%	40.9%	23% decrease
GI clinic visits (total n)	181	207	13% increase

markedly, the mean length of stay remained relatively unchanged, decreasing by 3.6%. Also unremarkable was the percentage change in the number of admissions involving GI surgery, a small increase of 4.6% was noted. Finally, the total number of administrations of TPN (total parenteral nutrition) decreased by 4.3%.

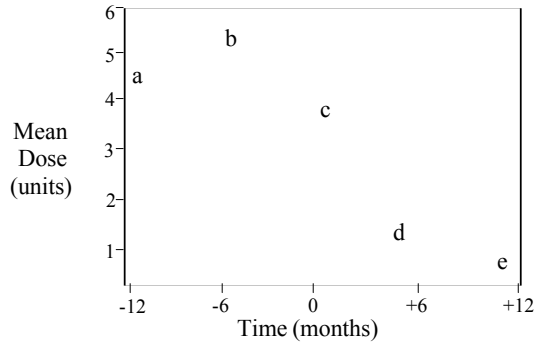

Figure 1. Mean daily dosage of prednisolone: a) 12 months before treatment with infliximab, b) 6 months before treatment, c) the week of treatment, d) 6 months after treatment and e) 12 months after treatment.

Results for the Steroid Data

The results based on the analysis of the steroid data for each patient are shown in Figures 1, 2 and 3. This study found that the mean daily dosage of prednisolone decreased during the 12 months post-infliximab therapy, when compared with the 12 months prior to therapy. Similarly, the mean daily dosage of budesonide decreased in the 12-month period after infliximab therapy (Figs. 1 and 3). Of note, as depicted in Figure 2, the weeks free of prednisolone increased in number after infliximab therapy.

DISCUSSION

The results of anti-TNF-α therapy in clinical trials for patients with CD demonstrate an exciting breakthrough in the medical management of inflammatory bowel disease. In addition, this study found a high response to infliximab, with 73.1% of patients studied being classed as responders. This is higher than the 66.6% of responders noted in clinical

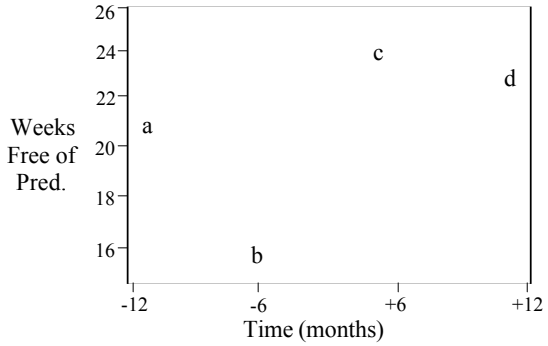

Figure 2. Total number of weeks free of oral corticosteroid prednisolone: a) 12 months before treatment with infliximab, b) 6 months before treatment, c) 6 months after treatment, d) 12 months after treatment.

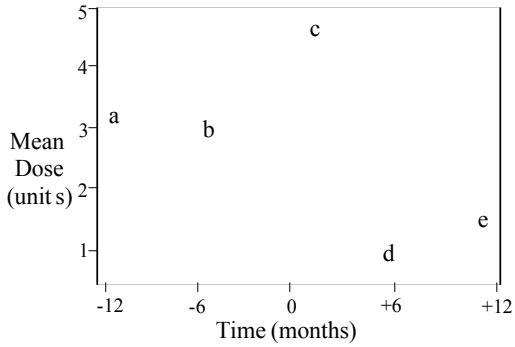

Figure 3. Mean daily dosage of locally-acting oral corticosteroid budesonide: a) 12 months before treatment with infliximab, b) 6 months before treatment, c) week of treatment, d) 6 months after treatment, and e) 12 months after treatment.

trials. Possible reasons for this difference could be that the sub-group analysed in this report may not have included some of the patients with a more resistant or complicated disease. The majority of the patients had a very active disease, as shown by the mean CDAI, 267.97 ± SE 24.08. Indeed, the maximum value for CDAI in the subgroup of patients was 514.8. It is interesting to note that 42.3% of patients were either current smokers or had a history of smoking, as smoking has previously been implicated in the pathogenesis of Crohn's disease.

Medical economics since the 1990s has concentrated on the delivery of quality medical care to all patients while trying to minimise costs.[6] The Hay and Hay analysis of 1992 calculated that hospitalisation and surgery accounted for most of the annual medical costs associated with CD.[7] One might therefore conclude that any treatment that reduces the number of surgical hospitalisations should decrease both the cost of Crohn's disease admissions and the overall costs. Infliximab is an expensive medication, (over £1200 IR per infusion of the medication) thus, its impact on health-care usage has major implications. Thus, the findings of this study are exciting, in that, after infliximab therapy, the number of admissions to hospital decreased markedly, by 46.9%. It is interesting to note that the number of procedures such as radiological investigations and endoscopies also decreased; perhaps each patient's symptomatic improvement after infusion of infliximab reduced the need for performing investigations. Of note, surgical procedures increased in frequency post-infliximab, as did GI clinic visits. Indeed, surgery is the final option in many patients who fail to respond to infliximab. It would be stimulating to further analyse the economic data, perhaps subdividing it into patients who responded to treatment and those who did not.

Steroids are commonly employed in the treatment of acute flare-ups of chronic active disease. Although they are effective, they are associated with problems, such as the development of steroid-dependent or steroid-resistant disease, and the prevalence of unpleasant side effects including: truncal obesity, easy bruising, gastro-intestinal upset, moon-shaped facies, striae and even psychotic episodes. A particularly sinister side effect of steroids is the increased risk of developing osteoporosis in later life. Thus, any treatment that reduces the prescription of corticosteroids will enhance their efficacy in future use and decrease the incidence of severe side-effects. As depicted in Figures 1 and 3, the mean daily dosages of prednisolone and budesonide increased immediately prior to treatment with infliximab, indicating the development of active disease. Subsequent to therapy with infliximab, the mean daily dosage decreased. This would support the postulate that infliximab has a "steroid-sparing" role. Figure 2 almost mirrors these results, as the mean number of weeks free of standard oral steroids (prednisolone) increases post-infliximab.

CONCLUSION

The findings from this study of 25 patients with chronic active CD are comparable to those previously achieved in the controlled setting of clinical trials. Infliximab has been shown to reduce the overall use of health care, especially the total number of admissions to hospital. This suggests that infliximab therapy, although expensive, may actually reduce the overall cost of Crohn's disease. In addition, subsequent to treatment with infliximab, corticosteroids in general were prescribed less, thus supporting the theory that infliximab acts as a steroid-sparing agent. Further investigation into the impact of infliximab on health-care usage and the prescription of corticosteroids could be an exciting and challenging field for research in the future.

ACKNOWLEDGEMENTS

I would like to thank all who participated in this study, in particular Dr. Maria O'Sullivan and Prof. C. O'Morain for all their support and guidance. I also wish to acknowledge the Health Research Board (HRB) for funding this study.

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