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ORIGINAL ARTICLE

Observational Study

Clinical and economic impact of infliximab one-hour infusion protocol in patients with inflammatory bowel diseases: A multicenter study

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Abstract

AIM

To assess the impact of short infliximab (IFX) infusion on hospital resource utilization and costs.

METHODS
All inflammatory bowel diseases (IBD) patients who received IFX 1 h infusion from March 2007 to September 2014 in eight centers from Southern Italy were included in the analysis. Demographic, clinical and infusion related data were collected. The potential benefits related to the short infusion protocol were assessed both in terms of time saving and increased infusion unit capacity. In addition, indirect patient-related cost savings were evaluated.

RESULTS
One hundred and twenty-five patients were recruited (64 with ulcerative colitis and 61 with Crohn's disease). Median duration of disease was of 53 mo and mean age of pts at diagnosis was of 34 years (SD: ± 13). Adverse infusion reactions were reported in less than 4% both before and after short infusion. The total number of infusions across the selected centers was of 2501 (30.5% short infusions). In the analyzed cohort, 1143 h were saved (762 in the infusion and 381 in observation phases) through the rapid IFX infusion protocol. This time saving (-15% compared to the standard protocol in infusion phase) represents, from the hospital perspective, an opportunity to optimize infusion unit capacity by allocating the saved time in alternative cost-effective treatments. This is the case of opportunity cost that represents the value of forgone benefit which could be obtained from a resource in its next-best alternative use. Hence, an extra hour of infusion in the case of standard 2-h IFX represents a loss in opportunity to provide other cost effective services. The analysis showed that the short infusion increased the infusion units capacity up to 50% on days when the IFX infusions were scheduled (infusion phase). Furthermore, the analysis showed that the short IFX infusion protocol leads to time savings also in the post-infusion phase (observation) leading to a time saving of 10% on average among the analyzed centers. Finally, the short infusion protocol has been demonstrated to lead to indirect cost savings of €138/patient (average -€17.300 on the whole cohort).

CONCLUSION
A short IFX infusion protocol can be considered time and cost saving in comparison to the standard infusion protocol both from the hospital's perspective, as it contributes to increase infusion units capacity, and the patients' perspective, as it reduces indirect costs and the impact of treatment on everyday life and work productivity.

Key words: Infliximab; One-hour infusion; Cost savings; Economic impact; Multicenter study

Core tip: Infliximab (IFX) is a monoclonal antibody anti-tumour necrosis factor used in the treatment of moderate-to-severe inflammatory bowel diseases refractory to conventional therapy. It is usually administered *i.v.* at a dose of 5 mg/kg as a 2-h infusion. Shortening the infusion protocol to 1 h is equally safe and positively affects quality of life. This paper analyzes the impact of short IFX infusion on hospital resource utilization and costs, both in terms of time saving and increased infusion unit capacity. In addition, we provide evidence of indirect patient-related cost savings.

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INTRODUCTION

Infliximab (IFX) is a chimeric monoclonal antibody anti-tumour necrosis factor (anti-TNF) effective in inducing and maintaining remission of moderate to severe luminal and fistulizing Crohn's disease (CD)[1,2] and of moderate to severe refractory ulcerative colitis (UC)[3]. It is also used to treat rheumatoid arthritis and moderate to severe psoriasis[4,5]. IFX is usually administered intravenously at a dose regimen of 5 mg/kg as a 2-h infusion followed by a monitoring time of 2 h thereafter[6-8]. This standard practice has been adopted in order to minimize infusion reactions, which are known to occur during infusion and later in the immediate post infusion period)[9] However, the standard practice has a significant impact in the setting of limited healthcare resource in terms of dedicated areas (infusion units), facilities and, mostly, time. Short infusion (1-h) protocols have been found safe in patients with rheumatoid arthritis[10]. Recently, a shorter infusion time of one hour has been used also in inflammatory bowel diseases (IBD) patients, in maintenance therapy and who tolerated a 2-h infusion without adverse events, in referral centers[11,12]. Tolerability of one hour infusion has also been reported for 10 mg/kg IFX[13]. One hour infusions are less time-consuming and might be considered in clinical practice to improve patients' quality of life and compliance to IFX therapy[14]. Moreover, infusion therapy is also costly for patient in terms of expenses related to travel to the hospital and of hours spent in the infusion clinic (work loss). At present evidence on cost savings of short infusion is scanty. We have previously confirmed in a pilot study[15] that shortening the infusion protocol to 1 h is equally effective and safe than standard protocol. The aim of the present study was to assess the impact of short IFX infusion on hospital resource utilization and costs in a multicenter study from eight referral centers in Italy.

MATERIALS AND METHODS

All patients who received 1 h infusion of IFX from

Table 1 Traditional *vs* short infusion protocols time duration

	Traditional infusion (min)	Short infusion (min)
Observation phase	90	60
Infusion phase	120	60
Total minutes	210	120
Total hours	3.5	2

March 2007 to September 2014 in eight centers from Southern Italy were included in the analysis. Written informed consent was obtained prospectively from each patient. For each patient, demographic, clinical and infusion related data were collected retrospectively on a shared dedicated database (Excel). All patients received the dose of 5 mg/kg. Optimization of therapy was achieved by shortening the interval between infusions.

On the basis of available data, the potential benefits related to the short infusion protocol were considered both in terms of potential time saving and increased infusion unit capacity. As there was no difference in terms of drug costs, nursing and specialist service costs in both protocols, it was not possible to assess the short infusion protocol impact in direct costs terms. Instead, it was possible to estimate the related productivity loss/gain of the two different protocols. Indirect costs were expressed in terms of working hours lost due to the infusion. Indirect costs were calculated on the basis of productivity lost according to the human capital approach. The value was collected through available literature[16]. In particular, the indirect costs were calculated by multiplying infusion hours by work/hour/loss in order to assess the difference between the two different protocols. Details on infusion time for both protocols are reported in Table 1. Furthermore, we assessed the impact related to the short infusion protocol on the units capacity in term of number of treated patients; a questionnaire was sent to the participating centers to collect data on the number of patients submitted to IFX infusion/day by adopting the short infusion schedule which was compared with the same data when a standard infusion time was used. This comparison was possible just in one center (University Hospital Palermo); because of different work organization, this value was not available in other centers. Continuous variables were expressed as mean ± standard deviation, and categorical variables as absolute frequency and percentage. The comparison between continuous variables was made by the Student *t*-test and categorical variables were analysed by using the chi-square test. Statistical significance was reached when P was < 0.05. Data were analyzed using the statistics software SPSS version 15.0.

RESULTS

A total of 125 patients with IBD were included in the study, 64 with UC and 61 with CD. Seventy-one (61.6%) were male and 48 (38.4%) were female. Mean age of patients at diagnosis was 34 years (SD: ± 13). Characteristics of the patients are given in Table 2. Median duration of disease was of 53 mo (IQR: 16-110.5) and median duration of follow-up was 34 mo. The mean number of total infusion/patient was 20 (range: 4-60) and the mean number of short infusions was 6.1 (range: 1-19). Patients were shifted to one-hour infusion after a median interval of 21 mo. Median follow-up of patients in short infusion was 12 mo. Indications for IFX were steroid-dependence in 61.6%, steroid-resistance in 8%, failure of thiopurines (9.6%), fistulizing disease (5.6%), rescue therapy in severe UC (2.4%). A total of 33 patients (26.4%) were taking steroids. Concomitant use of immunomodulators (azathioprine or methotrexate) was reported in 28 patients (22.4%). Seventy-five patients received mesalamine.

Table 2 Demographics and characteristics of patients

Gender	
Male	77 (61.6%)
Female	48 (38.4%)
Mean age at diagnosis	33.6 (range: 10-80)
Smoke	
No	76 (70.8%)
Yes	26 (20.8%)
Former	23 (18.4%)
Family history	
No	106 (84.8%)
Yes	19 (15.2%)
Appendicectomy	
No	116 (92.8%)
Yes	9 (7.2%)
Characteristics of disease	
Ulcerative colitis	64 (51.2%)
Crohn's disease	61 (48.8%)
Duration of disease at 1st infusion (median)	52 mo (IQR: 16-110.5)
Duration of follow-up (median)	34 mo (IQR: 19-55.5)

Fifty-seven (45.6%) patients received no premedication. A total of 68 patients (54.4%) was submitted to premedication: 51 (40.8%) with steroids, 1 with antihistaminic (0.8%) and 16 patients with both (12.8%). Details are reported in Table 3.

Adverse infusion reactions were observed in about 4% of patients both before (4 patients) and after short infusion (5 patients). Among the 9 patients who experienced an infusion reaction we recorded 7 being acute, 1 acute-severe, 1 delayed. Adverse infusion reactions occurred at a median of 3 (IQR 3-23) mo after the first infusion. In patients with mild or moderate infusion reaction the infusion was interrupted, medical therapy was administered and after resolution of symptoms, infusion was restarted slowly. The use of premedication was not significantly associated with different rates of infusion reactions. Opportunistic infections occurred in 5 patients (4%) both before and after short infusion. Opportunistic infections occurred at a median of 32 (IQR: 18-39) mo after the first infusion. No death occurred. Details are given in Table 3.

The total number of infusions across the selected centers was of 2501 (30.5% short infusions). We therefore calculated the potential related benefits both in

Table 3 Indication for biologic, concomitant therapies and premedication

Patients treated with IFX (total 125)	
Indication for IFX	
Steroid-dependent	77 (61.6%)
Steroid-resistant	16 (12.8%)
Rescue therapy severe UC	3 (2.4%)
EIM	0
Failure of thiopurine	12 (9.6%)
Fistulizing disease	7 (5.6%)
Prevention of postoperative recurrence	1 (0.8%)
Indication for IFX (dual indication)	
Steroid-dependent + EIM	3 (2.4%)
Steroid-dependent + failure of thiopurine	3 (2.4%)
Steroid-dependent + fistulzing disease	1 (0.8%)
Fistulizing disease + EIM	2 (1.6%)
Total infusions (mean)	20 (range: 4-60)
Short infusion (mean)	6.1 (range: 1-19)
Concomitant therapies	
None	12 (9.6%)
Steroids	25 (20%)
Thiopurine	10 (8%)
Methotrexate	2 (1.6%)
5ASA	56 (44.8%)
Concomitant therapies (polipharmacy)	
Steroids + thiopurine	1 (0.8%)
Steroids + 5ASA	4 (3.2%)
Steroids + thiopurine + 5ASA	3 (2.4%)
Thiopurine/methotrexate + 5ASA	12 (9.6%)
Total use of steroids	33 (26.4%)
Total COMBO therapy (Thiopurine or Mtx)	28 (22.4%)
Total use of mesalamine	75 (60%)
Premedication	
None	57 (45.6%)
Steroids	51 (40.8%)
Antihistaminic	1 (0.8%)
Steroids + antihistaminic	16 (12.8%)
Time of premedication	
None	57 (45.6%)
From first infusion	65 (52%)
From second Infusion	3 (2.4%)
Only short infusion	0

IFX: Infliximab; EIM: Excitability-inducing material; UC: Ulcerative colitis; 5ASA: 5-aminosalicylates.

terms of time saving and increased infusion unit capacity. In the analyzed cohort, 1143 h were saved (762 in the infusion and 381 in the observation phase) through the rapid IFX infusion protocol. This time saving (-15% compared to traditional protocol in infusion phase) represents, from the hospital perspective, an opportunity to optimize infusion unit capacity by allocating the saved time in alternative cost-effective treatments. This is the case of opportunity cost that represents the value of forgone benefit which could be obtained from a resource in its next-best alternative use. Hence, an extra hour of infusion in the case of standard 2-h IFX represents a loss in opportunity to provide other cost effective services. The analysis showed that the short time infusion increased the infusion units capacity up to 50% on days when the IFX infusions were scheduled (infusion phase). In the center which provided the data, by using the one-hour infusion protocol, the number of patients treated per day increased from 3 to 6 (a 50% increase), leaving enough time to schedule additional therapies such as *i.v.* iron infusions. Furthermore, our analysis showed that the short IFX infusion protocol leads to time savings also in the post-infusion phase (observation) by leading to a time saving of 10% on average among the analyzed centers. Finally, the short infusion protocol has been demonstrated to lead to indirect cost savings of €138/patient (average -€17.300 on the whole cohort). In Table 4 we report the details on the split between short and traditional infusion.

DISCUSSION

IFX therapy is effective in the management of IBD both in the induction and in maintenance of remission, in preventing the rate of postoperative recurrence in CD and in reducing the need of hospital admission and surgery. Recently, IFX therapy has been shown to promote mucosal healing, an outcome strongly related to long-term remission[17]. This treatment is widely used, since about 15%-20% of patients with IBD are currently on anti-TNFs and usually for long periods of time since most patients will be kept on maintenance therapy[18] for 12-24 mo or even longer. IFX is administered at a dose of 5 mg/kg as a 2-h infusion followed by a monitoring time of additional 2 h. Efficacy and safety of shorter IFX infusion times have been recently demonstrated both in the setting of rheumatological disorders and IBD in observational studies. A good tolerability profile of one-hour infusion (3 or 5 mg/kg) was reported first in rheumathoid arthritis, psoriasic arthritis and ankilosyng spondylitis patients[10,19] and recently for IBD patients who tolerated a 2-h infusion without adverse reactions (acute or delayed)[20]. A meta-analysis has confirmed that rapid IFX infusions of $\leqslant$ 1-h duration are safe and not associated with increased risk of infusion reaction when compared to standard infusions in patients with IBD, rheumatoid arthritis, spondylarthoparthy and psoriatic disease[20].

Short IFX infusion could also influence patients' quality of life. Principi *et al*[14] reported an improvement in social and job quality of life in patients treated with 1-h infusion of IFX. However, though some Authors[21] have suggested the possibility of reducing costs for the healthcare provider of patient daycare attendance combined with medical staffing requirements, a pharmacoeconomic evaluation of the accelerated infusion protocol has never been approached. To our knowledge, data in the literature on economic impact of one-hour infusion in IBD patients comparing standard infusion are scanty. Only one study, carried on in the United States, has been published so far, enrolling patients on accelerated infusions (both 90 min and 60 min long) at various IFX dosage[22]. This study focused on hospital cost savings, by estimating the cost required to deliver infusions over 120-min *vs* using the accelerated infusion times: 118 h of infusion time and $53632 were saved by using the accelerated protocols ($P < 0.001$).

Kuin *et al*[23] evaluated both safety and costs of home-

Table 4 Infusion time and indirect cost savings: Traditional *vs* short infusion protocol

	w/out SI (min)	w SI (min)	Delta (min)	Saving (min)	Delta %	Hours	Saving indirect costs (€)
Infusion time	300120	254400	-45.72	-45720	-15%	-762	-11.525
Post infusion time	225090	202230	-22.86	-22860	-10%	-381	-5.763
Total time	525210	456630	-68.58	-68580	-13%	-1143	-17.288
Costsaving/patient						-9	-138

based IFX infusion as an alternative to hospital-based infusions for the management of CD patients. Home-based IFX infusions were associated with a cost saving of €55 per infusion. Another study, conducted in a small pediatric population in United States, obtained similar results[24]. Home-based therapy, though fascinating, is not applicable to all health care systems. In Italy, there are also regional differences.

Our findings suggest that in terms of indirect costs a short IFX infusion protocol in the hospital can be considered time and cost saving in comparison to the traditional infusion protocol. Our analysis could not assess differences in direct costs since costs of devices and hospital staff were similar whatever protocol is used.

The strengths of our study are: Firstly, the assessment of indirect costs of the two different infusion protocols which has never been approached and that is the most relevant from the patients' perspective; secondly, the evaluation of the improvement of organizational efficiency in terms of health care utilization resources. The use of short infusions seems to increase the unit capacity up to 50%, though this evaluation was possible only in one of the participating centers.

Our study has however some limitations. Firstly, the impact on hospital resource utilization was assessed in only one center. It could be argued that this result may not be representative of all the involved centres as it depends also on hospitals' specific organizational features. Secondly, the retrospective methodology of our study could influence the accuracy of the results. However, detailed notes of infusion characteristics were made at the time of each infusion in all participating centers so that underreporting was not expected. Finally, an activity based costing approach would be recommended in order to assess the "real" direct cost impact from the hospital perspective.

In conclusion, this study can be considered an important step in the economic evaluation of the short infusion protocol within the Italian context, although it would be recommended to perform a full economic evaluation considering both costs and related outcomes in order to provide comprehensive evidence based data useful for decision makers at local level.

A short IFX infusion protocol can be considered time and cost saving in comparison to the standard 2-h infusion protocol as it contributes to increase infusion units capacity up to 50%. From the patients' perspective, reduces indirect costs and the impact of treatment on everyday life and work productivity. On the basis of our study, we believe that the one hour IFX infusion protocol in patients in stable maintenance therapy should be implemented in clinical practice.

COMMENTS

Background

Infliximab (IFX) is a chimeric monoclonal antibody anti- tumour necrosis factor effective in inducing and maintaining remission of moderate to severe luminal and fistulizing Crohn's disease and of moderate to severe refractory ulcerative colitis. It is also used to treat rheumatoid arthritis and moderate to severe psoriasis. IFX is usually administered intravenously at a dose regimen of 5 mg/kg as a 2-h infusion followed by a monitoring time of 2 h. This standard practice has been adopted in order to minimize infusion reactions. Previous reports have shown that shortening the infusion to one hour is equally safe. The key-question addressed by this manuscript is whether this accelerated infusion protocol is cost-saving both on the hospital's and on the patient's perspective.

Research frontiers

Data in the literature on economic impact of one-hour infusion in inflammatory bowel diseases patients are scanty. Only one study, carried on in the United States, focused on hospital cost savings, by estimating the cost required to deliver infusions over 120-min *vs* using the accelerated infusion times.

Innovations and breakthroughs

The methodology adopted in this research explores the potential benefits related to the short infusion protocol both in terms of potential time saving and increased infusion unit capacity. Indirect costs were expressed in terms of working hours lost due to the infusion. This approach has been recently applied in pharmacoeconomic research.

Applications

The future application of the research could be the use of the accelerated infusion protocol not only with the infliximab originator molecule, but also with biosimilars. This could significantly reduce direct and indirect costs, increase infusion units' capacities and allow access of increased number of patients to effective therapy even in low income countries.

Terminology

Standard infusion practice requires dedicated areas (infusion units), facilities and time. Saving time is an opportunity to optimize infusion unit capacity by allocating the saved time in alternative cost-effective treatments or by increasing the number of treated patients. Indirect costs reflect patients' expenses related to travel to the hospital and of hours spent in the infusion clinic (work loss).

Peer-review

Manuscript is well written and easy to follow.

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