Pattern of use, economic burden and vial optimization of infliximab for rheumatoid arthritis in Italy

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Abstract

Objective

The aim of this study was to retrospectively examine the pattern of utilization in clinical practice and the costs of therapy of infliximab in the treatment of refractory rheumatoid arthritis (RA).

Methods

Ninety-five RA patients (22 newly treated and 73 maintenance patients) who received at least one infliximab infusion during a selected observation period of one year were studied. After induction phase, infliximab was given at initial dose of 3 mg/kg every 8 weeks. Based on clinical efficacy measured by Disease Activity Score 28 (DAS 28) index, dose adjustments were performed by increasing pro kg dose and/or reducing infusion interval. Overall one-year's treatment costs were also examined.

Results

Sixteen (17%) out of 95 patients discontinued treatment before the end of the study owing to lack of efficacy (15) or adverse events (1). Thirteen (59%) out of 22 newly treated patients experienced treatment escalation in the first year of therapy by increasing dose (13.6%), reducing interval (9%), or both (36.3%). The mean infliximab dose administered to all the patients was 3.57 mg/kg and the mean infusion interval was 50 days. Considering all expenditure items, the mean year treatment cost per patient was €8454,65. Infliximab vial optimization allows us to reduce this amount to €7505,85, with a significant saving of €948,80 per patient/year.

Conclusions

In this observational study, adjustments in infliximab treatment in the first year of therapy were common. Despite dose escalation, the mean dosing schedule does not significantly differ from those recommended in the product label. The cost of treatment could be reduced by using infliximab vial optimization.

Key words

Infliximab, rheumatoid arthritis, anti-TNF-α, dose, treatment, cost, vial.

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Introduction

The spectrum of therapeutic options for the treatment of rheumatoid arthritis (RA) has deeply changed during the last few years as a result of the introduction of biological drugs.

Several randomised clinical trials and post-marketing experience with TNF-α blockers have demonstrated a significant improvement in clinical signs and symptoms, functional and general health status, and prevention of radiographic damage in patients with severe and refractory RA (1-3).

Based on the results of the ATTRACT study (4), in 1999, the US Food and Drug Administration (FDA) approved infliximab, a chimeric monoclonal antibody targeting human TNF-α, for the treatment of RA, in combination with methotrexate. According to the product label, infliximab is administered by intravenous infusion using a loading dosage of 3 mg/kg given at weeks 0, 2 and 6, followed by administration every 8 weeks thereafter.

Despite the impressive efficacy of infliximab standard dosing protocol in clinical trials, in the same studies, higher doses and/or more frequent dosing suggested a potential for additional improvement (5). These results and clinical experience led to the concept of infliximab treatment escalation as an approach aimed to reduce the incidence of incomplete clinical response.

The experience of many clinical trials demonstrated the efficacy of increasing infliximab dose over 3 mg/kg (usually to 5 mg/kg and over) and reducing the infusion maintenance interval to under 8 weeks (6-8).

In the first post-marketing period, since 2001, infliximab therapy in Italy has been necessarily related to the ANTARES Project (9), an observational study planned by the Italian Society of Rheumatology, that collected data from all RA patients treated with biological drugs from 2001 to 2004.

The ANTARES Project was designed to standardize the use of TNF-α blockers in severe refractory RA by selected Rheumatology Units and to establish guidelines for the selection of eligible patients. Moreover, this trial strictly regulated dosage and schedule of administration of each drug as indicated in the product label.

By the end of the ANTARES Project, Italian rheumatologists could prescribe biological drugs without the restrictions of the clinical trial. This condition led to a progressive increase of eligible RA patients and to the possibility of adapting the anti-TNF-α (especially infliximab) dosing schedule to the single patient.

Obviously, this new scenario can produce an increase in drug consumption and consequently in infliximab administration costs.

However, we have recently audited our practice in the use of infliximab and have found imaginative ways of reducing wastage of an expensive resource such as vial optimization of patients infused at the same time.

To date, there are no data in Italy showing the average infliximab dose and dosing interval used to treat RA in a usual clinical setting. Furthermore, many physicians overestimate the real measure of dose escalation and the actual cost of an infliximab infusion.

Therefore, we conducted a retrospective analysis of one year's utilization of infliximab in RA patients in our daily clinical practice, with the aim of better understanding the pattern of use of this anti-TNF-α in our Rheumatology Unit (with an emphasis on treatment escalation) and quantifying the true infliximab economic impact in the management of RA in Italy, from a health-care system perspective.

Patients and methods

Study sample selection

We performed an observational retrospective study based on the Gaetano Pini Institute database of patients treated with biological drugs.

The analysis included all RA patients aged ≥18 years (fulfilling the American College of Rheumatology Criteria (10)) who received at least one intravenous infusion of infliximab in a selected period of 365 days, from May 2003 to April 2004. Patients were excluded if they had one or more medical claims with a listed diagnosis of psoriatic arthritis or ankylosing spondylitis during their history. These exclusion criteria were implemented to avoid including

in the study sample patients who have might received infliximab for another disease (because dosing may be different for these indications as compared with RA).

We obtained a study group of 95 patients who had received a total of 590 infusions of infliximab throughout the observation period.

Study outcomes

Infliximab is dispensed in 100 mg vials in powdered form; we used vials of sterile water (10 ml) to reconstitute the infliximab powder and then 250-ml bags of normal saline for the infusion. After the reconstitution, infliximab may be conserved at 2-8°C for a maximum of 24 hours before the administration.

Applying standard guidelines for RA patients, infusions were initially given on day 0, 15, 45 and then every 8 weeks, starting at the infliximab recommended dose of 3 mg/kg.

At the time of initiation of infliximab, data were recorded on age, weight, duration of disease, concomitant disease modifying anti-rheumatic drugs (DMARDs) treatment, and disease activity (measured by Disease Activity Score 28 [DAS 28]) for each patient (11). For every infusion, data on efficacy, infusion interval, infliximab pro-kg dose, side effects and treatment discontinuations were collected.

Clinical response was evaluated at each infusion by variation of DAS 28 values versus baseline. We considered patients with reduction of DAS 28 > 1.2 as good responders, with reduction between 0.6 and 1.2 as moderate responders, and with reduction < 0.6 as non responders (12).

For moderate and non responder patients, physician decided to modify infliximab schedule by progressively increasing pro-kg dose from 3 to a maximum of 5 mg/kg and/or by reducing the infusion interval from 8 to a minimum of 6 weeks. (13, 14)

For persistent (at least 6 months) good responders, the interval between infusions was progressively increased from 8 to a maximum of 12 weeks, whereas the pro-kg infliximab dose was never reduced under 3 mg/kg.

We calculated all the costs, measured in euro, of this therapy with the aim of establishing the cost for each infusion and the economic burden of one year's treatment with infliximab.

The cost per vial of infliximab during the observational period was €496,49; we counted the cost of concomitant DMARDs treatment (in terms of therapy days) based on the national pharmaceutical tariffs, too.

The consumption of health-care resources needed for the infusions covered all possible expenditure items required to complete the treatment (nursing and medical staff, material required for intravenous infusion, and waste disposal).

The cost of nursing and medical staff required for each infusion was calculated considering their cost per minute and the mean salary of Lombardy hospitals (15). At the moment of our analysis, the mean annual salary of a professional hospital nurse was €39,000, and we assumed that she works 1512 hours per year (36 h/week for 42 working weeks/yr), with a per-minute cost of €0.43. The mean annual salary of a National Health System (NHS) rheumatologist was about €83,000, and we assumed that he works 1428 hours/year (34 h/week for 42 weeks/yr, not including 4 h/wk for updating), giving a per-minute cost of €0.97.

Based on direct observations at our Rheumatology Unit and bearing in mind that in our hospital the high volume of patients leads to the simultaneous infusions of several patients, we estimated that each infusion required 20 and 15 minutes for the nurses and doctors, respectively.

The estimated cost of materials used to perform each infusion, including sterile water for the drug reconstitution, saline solution for dilution, drip kit, cotton wool, disinfectant, rubber gloves, butterfly needle and syringe, was also calculated.

The cost of waste disposal was estimated at €0.96 /kg (incl. VAT) (15).

We then added 20% for overheads, on the basis of sample surveys in some hospitals in the Lombardy region.

Statistical analyses

Demographic and clinical characteristics of the study sample were summarized, including age, gender, disease duration, DMARDs therapy history, and disease activity.

Descriptive statistics including mean, standard deviation, and median on infliximab initial and last dosing (pro kg dose and infusion interval), infusion related costs, and one year's treatment total cost.

All data were analyzed using the statistical software SPSS® (SPSS Inc, Chicago, Illinois, version no. 11). Statistical comparison between sample subgroups were undertaken using an unpaired *t*-test, while differences in initial versus last mean dose of infliximab were assessed using a paired-sample Student's *t*-test.

Results

Study population

A total of 95 RA patients received at least one infliximab infusion throughout the study.

Of these, 73 were already receiving infliximab at the start of the observation period from a median time of 606 days, and continued on the maintenance schedule. The other 22 patients started taking infliximab during the observation period, receiving first of all the induction phase established by the normal therapeutic schedule, involving three infusions at shorter intervals (days 0, 15 and 45).

During the observation period, in the *de novo* subgroup 5 (22.7%) out of 22 patients stopped infliximab treatment because of lack of efficacy (4 patients, 18.1%) or adverse events (1 patient, developed Legionella pneumonia, 4.5%).

In the maintenance group, 11 (15%) out of 73 patients stopped the therapy, all because of lack of efficacy. In the whole series, 16 (17%) out of 95 patients discontinued infliximab before the end of the study.

All the demographic characteristics of the study population are summarized in Table I.

The mean (±SD) age of the whole group was 57 (±7.8) years, with more than 60% of patients aged between 50 and 70 yrs. There was a large majority of women (86.5%). Mean body weight was 63 kg. The mean duration of the disease was 13.9 (± 4.4) years (15.3

Table I. Demographic characteristics of study population.

	Mean ± SD		
	De novo patients	Maintenance patients	All patients
Age (yrs)	56.25 (± 7.5)	57.48 (± 7.9)	57.27 (± 7.8)
Disease duration (yrs)	9.3 (± 3.7)	15.3 (± 4.7)	13.9 (± 4.4)
Sex (M/F)	5/19	8/64	13/82
N° of previous DMARDs	4.12 (± 0.83)	4.21 (± 0.89)	4.16 (± 0.85)
DAS 28 at baseline	4.73 (± 0.77)	5.30 (± 0.92)	5.16 (± 0,91)
Rheumatoid factor >10 IU/ml	80%	86%	84%

for patients already receiving treatment and 9.3 for those starting during the year). The most common reason for discontinuation of prior DMARD therapy was lack of efficacy, although a significant number of patients discontinued DMARD treatment due to toxicity.

At baseline, all patients had an active RA (DAS 28 >3.2), with a mean of 5.16 (5.30 for patients already receiving treatment, and 4.73 for those starting).

Consistently with the long duration of disease, patients had received multiple DMARDs before starting infliximab treatment (35.8% of patients had taken at least four different DMARDs and 67.9% at least three). Only 22.1% had taken fewer than three DMARDs before starting infliximab. All the patients had had at least three months of combination therapy with two or more DMARDs; 10.5% had had three-drug therapy, and 97.8% two drugs. The most frequent combination therapy was methotrexate plus chloroquine (34.7%).

Treatment analysis

We performed a total of 590 infusions of infliximab throughout the observation period. *De novo* patients received a total of 125 infliximab doses, while maintenance subgroup received a total of 465 infusions.

The mean ± SD infliximab dose at each infusion was 3.57 ± 0.57 mg/kg, with a weighted mean consumption per infusion of 227.29 ± 44.98 mg; these values differed significantly ($p < 0.0001$) between patients receiving maintenance treatment (3.63 ± 0.58 mg/kg, 227.16 ± 43.88 mg per infusion) and those just starting (3.36 ± 0.48 mg/kg, 227.76 ± 49.05 mg per infusion).

The mean ± SD interval between infusions throughout the study, reflecting the initial induction phase or the maintenance schedule, was on average shorter in the *de novo* patients (39.3 ± 15.5 days, 5.6 ± 2.2 weeks; median 43 days, 6.14 weeks) than in those already under treatment (52.8 ± 12.2 days, 7.5 ± 1.7 weeks; median 50 days, 7.14 weeks); the mean interval for the whole series was 50.0 ± 14.0 days (7.1 ± 2.0 weeks; median 49 days, 7 weeks).

The mean number of infusions per year was 5.68 in the *de novo* subgroup, 6.36 in maintenance patients, and 6.21 in all patients.

Analysis of treatment escalation was conducted only in the *de novo* patients with the aim of verifying changes in infliximab schedule during the first year of treatment.

Treatment escalation was defined as a decrease in the maintenance interval between infusions to < 7 weeks, an increase in the dose per kilogram of weight to > 3 mg/kg, or both. Using these criteria, 13 (59%) of 22 patients had a treatment escalation during the observation period; of these, 3 patients (13.6%) had only an increase in the dose, 2 patients (9%) had only a decrease in the interval, and 8 patients (36.3%) had both the conditions. In total, 11 patients (50%) had a dose increase and 10 (45.4%) had an interval decrease. In this subgroup, infliximab was started at a mean ± SD dosage of 2.99 ± 0.06 mg/kg (median 3.0 mg/kg, range 2.86 – 3.08 mg/kg), and at the end of observation period the mean dosage was 3.62 ± 0.59 mg/kg (median 3.58 mg/kg, range 2.86 – 5 mg/kg; $p = 0.0005$), with a percentage of increase from baseline of 21.4%. The mean ± SD time to dose escalation was 131.5 ± 36.3 days after the first infliximab infusion (median 137 days).

The analysis of interval infusion changes in maintenance subgroup showed that the mean ± SD interval started at 53.7 ± 14.1 days (7.6 ± 2.2 weeks; median 49 days, 7 weeks), and at the end of observation period the mean interval was 53.5 ± 13.9 days (7.5 ± 2.2 weeks; median 50 days, 7.14 weeks).

Starting from the mean infliximab dose per infusion, and considering that the drug is supplied in 100-mg vials, the mean number of vials employed per infusion should be therefore 2.61 for each patient. However, this figure, corresponding to a mean dosage of 261 mg, is purely theoretical, based on the hypothesis that each patient used the whole pack as required by the individual dosage, including what was left over after reconstitution.

Nevertheless, we have been able to demonstrate that, by ensuring that several patients are infused at the same time, we can reduce the number of vials required overall. Instead of discarding the portion of the vial not required, it can be used for another patient being infused at the same time.

Therefore, in our Rheumatology Unit, we planned infusions so as to optimize drug consumption. Thus, it seems therefore realistic to assume that the mean drug dose per infusion is the one in mg, corresponding to the real number of vials used.

Analysis of concomitant DMARD treatment showed that 87.5% of patients received MTX (median dose 12.5 mg/week), alone (81.5%) or in combination with other DMARDs such as cyclosporine and hydrossicloroquine (5.3%). Few patients (3.2%) were treated with cyclosporine alone and there were only isolated cases treated with leflunomide, gold salts or antimalarials as single-drug therapy.

Resource consumption

The costs of infliximab were calculated as a range from a minimum which was the cost of the drug actually administered by optimization of vials, to a maximum corresponding to the cost of the total vials which should have been used without optimization.

The mean infliximab cost per infusion ranged from €1078.90 to €1197.19 for

de novo subgroup, from €1144.03 to €1326.92 for maintenance subgroup, and from €1128.46 to €1295.89 for all patients.

The costs related to consumption of health-care resources needed for each infusion (with 20% added for overheads) were €14.94 (incl. VAT) for materials used to perform infusion, € 0.05 (incl. VAT) for waste disposal, and €8.60 and €14.95 for nursing and medical staff respectively, with a total cost of these items of €43.40.

Thus, the mean total cost per infusion ranged from €1122.30 to €1240.59 for *de novo* patients, from €1187.43 to €1370.32 for maintenance patients, and from €1171.86 to €1339.29 for the whole series.

Based on the number of infusions per year in each subgroup, we calculated the costs per patient of one year's therapy with infliximab. It ranged from €6593.50 to €7288.44 for *de novo* patients, from €7509.23 to € 8655.82 for maintenance patients, and from €7277.89 to €8317.69 for the whole series.

At the end, we estimated that the mean cost per patient of one year concomitant treatment with DMARDs was €227.96.

Total costs of one year's treatment with infliximab plus DMARDs ranged from €6821.46 to €7516.40 for *de novo* subgroup, from €7737.19 to € 8893.78 for maintenance subgroup, and from €7505.85 to €8454.65 for all patients (Table II)

Table II. Annual infliximab administration total cost per patient (€).

	Drug acquisition cost		All expenditure items	
	Optimized	Not optimized	Optimized	Not optimized
De novo patients	€ 6593.50	€ 7288.44	€ 6821.46	€ 7516.40
Maintenance patients	€ 7509.23	€ 8655.82	€ 7737.19	€ 8893.78
All patients	€ 7277.89	€ 8317.69	€ 7505.85	€ 8454.65

Discussion

Several well-designed randomised clinical trials have definitely shown that infliximab has an impressive efficacy in the treatment of early and long-standing refractory RA.

Although the recommended dosing schedule for infliximab is at the lower end of doses that were evaluated in these clinical studies, pharmacokinetic modelling has suggested that treatment escalation, either decreasing the interval between infusions or increasing infliximab pro-kg dose, may result in improved efficacy.

Therefore, we conducted a retrospective analysis to characterize the pattern of infliximab utilization in Italy and to establish the economic burden of one year's treatment with infliximab.

We treated 95 RA patients performing 590 infliximab infusions during the study period. Although the size of the cohort was modest, we believe this is a group which is representative of a "real life" clinical practice. In fact, most of the patients had long-standing RA (mean disease duration 13.9 years) with multiple DMARDs failure (mean 3.4) and high disease activity (mean DAS 28 5.16, with all patients having a DAS 28 > 3.2).

Sixteen patients stopped infliximab treatment throughout the observational period (5 in the *de novo* subgroup and 11 in the maintenance subgroup). The rate of discontinuation in the *de novo patients* was 22.7%, not significantly different from the proportion of discontinuation at 1 year reported in the ATTRACT trial (22%) (4), but higher than the one reported by Stern and Wolfe (14%) (21).

In the last few years the question of infliximab dose escalation as an effective approach to an inadequate clinical response has become very suggestive.

Ariza-Ariza *et al*. (22) recently published a systematic review of literature performed to estimate the frequency of this therapeutic approach. Their analysis of 15 reports demonstrated that 53.2% of all infliximab patients needed a dose escalation during the first year of treatment. The reported times elapsed to dose escalation ranged from 128 to 254 days.

In our cohort, treatment escalation during the first year was also very common, occurring in 59% (13 out of 22) of *de novo* patients treated with infliximab after a median time of 137 days of therapy. This approach was effective in 9 of them, while only 4 patients discontinued the treatment because of lack of efficacy despite dose intensification.

Patients in the maintenance subgroup (already treated with infliximab from a median time of 606 days at the moment of enrolment) did not require any dose escalation during the observation period. However, 11 of them, who had already experienced treatment escalation before enrolment, had to stop infliximab therapy because of lack of efficacy.

The magnitude of the dose increase, reported by Ariza-Ariza *et al*. as the percentage of increase from baseline, ranged from 29% to 43%, while in our cohort it was slightly lower (21.4%).

As an effect of dose intensifications, we registered in the de novo patients a significant increase of the mean infliximab dosage at the end of observation period (3.62 mg/kg every 7.1 weeks) compared to baseline. This value is exactly the same registered in the maintenance subgroup of patients (3.63 mg/kg every 50 days), determined by similar treatment escalations performed before study enrolment.

In conclusion, dose escalation starting from recommended dosage schedule of 3 mg/kg every 8 weeks occurs in the majority of patients and in more than half of cases this practice is necessary during the first year of treatment. However, in our cohort of patients the mean infliximab dose keeps significantly lower than the highest dosing schedule used in RA dose finding trials (up to 10 mg/kg) and in the treatment of other diseases such as ankylosing spondylitis, psoriatic arthritis or Crohn's disease (5 mg/kg).

Although infliximab dose intensification may be commonly used and beneficial in the treatment of patients who may not be responding optimally to infliximab therapy, it remains to be determined the economic impact of this higher drug consumption.

Total costs of one year's infliximab therapy was calculated including all

possible expenditure items required to complete the treatment, either the drug acquisition cost, or the consumption of health-care resource needed for the infusions (nursing and medical staff, material required for intravenous infusion, and waste disposal).

Obviously, infliximab acquisition cost (€1295.89 per infusion in all patients) is widely the most important item in the determination of the total treatment amount, while the burden of health-care consumption (€43.40 for each infusion) and concomitant DMARDs therapy (€227.96 per year) is much lower.

Considering all items, in our whole study group we estimated a mean year treatment cost per patient of € 8454.65. Analysis of subgroups revealed a much lower amount for the *de novo* patients (€7516.40) versus maintenance patients (€8893.78), as the expected result of the different infliximab dosing schedule.

A comparison with other data from international literature is not simple because infliximab acquisition cost differs significantly from one nation to another.

Weycker *et al*. (23) conducted a retrospective study with data from 2 large automated US health-care claims database, in which infliximab acquisition cost showed to range from $16.759 to $18.611 per year.

Gilbert *et al*. (24) examined economic impact of infliximab dose escalation in a population of 598 patients and demonstrated a mean year cost of $13.470, significantly higher in patients who experienced an increase in dose than in those with no change ($15.998 *vs*. $10.000; $p < 0.0001$). These findings are consistent with those reported by Ollendorf *et al*. (25), who showed an infliximab acquisition cost higher by more than 50% among patients with upward dose adjustment versus those without dose increase ($16.336 *vs*. $9.573; $p < 0.001$).

To date in the literature, there are no Italian data on the infliximab economic burden to compare with.

Since all biological therapies are costly and totally refunded by the state health-care service, we have looked at the ways of maximizing the use of these treatments whilst ensuring that eligible patients are treated.

As other authors recently demonstrated (26), we suggested that the cost of infliximab infusions with a vial optimization would reduce simply by ensuring that other patients were infused on the same occasion and an excess of the drug from one patient was used for another patient.

With the careful application of this policy, we have been able to keep drug wastage to a minimum and to reduce the yearly treatment cost per patient from €8454.65 to €7505.85, with a significant saving of €948.80 per patient/year. Applied to whole study population, it means the possibility of saving €90136.00 per year overall.

Because the current study is a retrospective analysis over a short period, it is difficult to accurately determine if patients received a prolonged benefit from infliximab dose escalation. Furthermore, we collected no data on changes in corticosteroids and methotrexate regimen during the observation period. However, our major focus for this study was simply to document the true magnitude of dose escalation in clinical practice and its real impact on the economic burden of infliximab therapy.

Finally, the cost estimates generated in this study did not examine the impact on overall direct and indirect medical costs from the use of infliximab, nor was this intended to evaluate the potential cost-effectiveness of this agent in the treatment of RA.

Despite the limitations noted above, we believe our study has important implications.

As indicated by the majority of authors, the results of our analyses confirm that also in Italian clinical practice infliximab dose escalation as the consequence of lack of efficacy is very common. In our experience, in half the patients this approach occurred in the first year of treatment and dose intensification was obtained by either dose pro kg increase or infusion interval shortening.

Despite this dose escalation, in our cohort, mean pro kg dose and mean infusion interval do not significantly differ from those recommended in the product label and, in the same way, the cost of one year's infliximab treatment does not significantly increase.

Given the high cost of acquisition of TNF-α blockers, vial optimization may be an important policy in the perspective of maximizing the use of scarce resources.

In fact, in our population of 95 patients, the amount of saving obtained by vial optimization may allow us to treat 10 more patients without an increase in the total expense.

Future prospective analyses should examine the cost-effectiveness of infliximab therapy, when used at the dosing schedule commonly applied in Italian clinical practice.

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