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Original article

Medication adherence and persistence in the treatment of rheumatoid arthritis with adalimumab and etanercept. Six years of analysis

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Abstract

Objective:
The aim of this study was to evaluate medication adherence and persistence of patients treated with Etanercept and Adalimumab for Rheumatoid Arthritis, also giving economic evaluations on therapy costs for Received Daily Dose (RDD).

Materials and methods:
This retrospective study took into account 6 years from January 1, 2007 to December 31, 2012. Medication adherence was quantified utilizing the ratio between RDD and Prescribed Daily Dose (PDD). Persistence has been reckoned taking into account the actual days of therapy comparing posology with supplied dose. The persistence has been graphed according to Kaplan-Meier method. The cost per RDD was reckoned starting from the expense incurred by Pescara General Hospital.

Results:
Medication adherence gave results in values between 0.88–0.97 for Etanercept and 0.83–0.90 for Adalimumab. The value of persistence was 100% for Etanercept and 90% for Adalimumab for the first year, and 70% for Etanercept and 80% for Adalimumab for the second year. In the 3rd year the persistence for Etanercept was 50% while for Adalimumab it was 60%. In the fourth year the persistence for Etanercept was 21% while for Adalimumab it was 27%. The statistical analysis was conducted using the Log rank test. The average cost per RDD was €32.97 for Etanercept and for Adalimumab it was €32.00 as an average of 6 years.

Conclusion:
The medication adherence was good for both Etanercept and Adalimumab. The rate of persistence decreased strictly in the fourth year of treatment. This data suggests the need for continuous monitoring of patients in treatment with TNF blockers.

Introduction

Rheumatoid arthritis (RA) is a complex autoimmune and progressive inflammatory disease that involves the joints and leads to their destruction[1]. The prevalence of RA is 0.5–1.0% in the general population worldwide[2,3]. Early and aggressive treatment with Disease-Modifying Anti-Rheumatic Drugs (DMARDs) is the cornerstone of initial therapy for RA. This therapeutic strategy has been shown to halt or prevent disease progression and joint destruction, and thereby to improve the outcome in RA patients[4]. The use of anti-tumor

necrosis factor alpha, Etanercept, Adalimumab, and Infliximab, started in 1990, has changed the treatment of RA[5]. Several trials have demonstrated the efficacy of these new drugs[6–9], but side-effects such as tuberculosis reactivation, serious infections and lymphomas must be monitored to understand the true effectiveness and safety for patients[10]. Adverse events are more likely than a lack of efficacy to result in drug discontinuation during the treatment[11]. The switching to another treatment due to adverse events or other reasons has a similar degree of response, i.e., the response achieved with the first agent was also achieved and maintained with the second agent[12]. Therefore, it is important to understand the real adherence to therapy by patients using TNF blocker[13–15], but there are no standardized methods to track persistence with and adherence to biologics. Out of 52 studies carried out in Europe and in the US, only one study reported measures of persistence, such as median drug survival and rates of discontinuation and retention. Four studies reported on adherence, all of which were conducted in the US and used administrative claims data[16]. For the study presented here the database used was made by pharmacists who dispense the drugs in the hospital pharmacy. The pharmacist, using pharmaceutical databases, tailoring educational information to individual patient needs, delivering technology-driven reminders to patients and providers, and integrating in-person interventions, is able to improve and measure the patient compliance[17,18]. Modifications in treatment regimes also have a direct impact on annual cost as well as on cost-effectiveness of these drugs, and this should be taken into account by health policy decision-makers[19]. The aim of this study is to describe the adherence and persistence to treatment using pharmaco-utilization parameters such as Received Daily Dose (RDD) and Prescribed Daily Dose (PDD), as well as to calculate the cost per day of therapy (cost per RDD) and then the annual cost spent on a single drug. The study involved only Etanercept and Adalimumab because Infliximab is administered intravenously in the hospital under medical supervision, while Etanercept and Adalimumab are managed by the patient at home. In Pescara Hospital are available all authorized anti-TNFa, then physicians can prescribe Anakinra, Rituximab, Golimumab, Certolizumab Pegol, but we consider for study only Adalimumab and Etanercept because they are used for the longest time.

Materials and methods

This retrospective study was realized by collecting data for 6 years, between 2007–2012, in Pescara Public Hospital (Italy). This hospital has 800 beds in total. The study design was approved by the hospital ethics committee of Pescara. Written consents were not given by the patients for their information because this is an observational retrospective study as regulated by the Italian Agency of the drug with the 'Guidelines for the classification and management of observational studies on drugs', as described in the guidelines available on the website 'agenziafarmaco.gov.it'. In the case of studies that do not involve a direct relationship with the patient, it is not necessary to administer the privacy of the patient and the informed consent form. The analysed data were already in the hospital pharmacy database used daily for the clinical practice. All data were analysed anonymously. Each patient was identified with a personal number. Patients were aware that their data were stored in a specific database, but were not informed that these data were used for research purposes. This procedure has been disclosed to the Ethics Committee that, in accordance with national legislation, approved it. The data of prescription and consumption of TNF alpha drugs was recorded in a database built specifically to follow the patient throughout the care pathway. In this database, called 'PharmaDDSS', the following data is recorded by the hospital pharmacist: patient demographics, drug used and its indication as prescribed by the physician. The hospital pharmacist collected these three parameters through consultation with the treatment plan completed by the physician, which is renewed every 6 months. Through the use of the specific database, PharmaDDSS, it is possible to understand the real PDD both as indicated by the physician and recorded by the hospital pharmacist. Each patient has their daily dose as indicated by the physician in their medical record. During the years prescribed doses of drugs can be changed by the physician and then updated by the hospital pharmacist, in this case of Etanercept and Adalimumab, only Etanercept dose could be changed by the physician, in fact for this drug are available two different dosages, 25 and 50 mg; Adalimumab dose can't be changed by a physician for authorized use. In this way, each patient has a personal record where all doses as indicated by the physician are recorded. The daily dose prescribed is the PDD. The RDD, instead, is calculated by dividing the dose received by the patient by the treatment days (Figure 1). The treatment days are considered as the difference between the first and second date of administration of the drug by the pharmacist in the hospital pharmacy. The RDD, in fact, can be defined as the dose really taken by the patient, and PDD represents the intention to treat. The optimum of medication adherence is 1. The drug persistence was calculated as

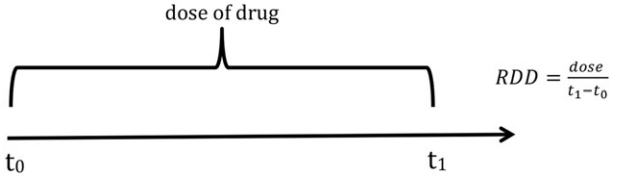

Figure 1. Calculation of received daily dose (RDD).

the total number of treatment days with the same drug for each patient. The drug persistence percentage was calculated for the following time intervals: <1 year, between 1–2, 2–3, 3–4, and >4 years. The Log-rank test was used to test the statistical difference of the two curves of survival. The cost per RDD was reckoned using a PharmaDDSS starting from the cost afforded by Pescara General Hospital in buying Etanercept and Adalimumab. The cost per year of treatment was calculated by multiplying the cost per RDD by 365 days.

Results

In the 6 years of analysis, from 2007–2012, 87 patients were analysed, 43 who used Etanercept and 44 Adalimumab. Patient characteristics: age, median and range, gender, actual days covered by drug treatment, median and range, are summarized in Table 1. Patients with RA are mostly female, and this figure is similar for both drugs under study. The age varies from 22–70 years, with the median around 50. This is in accordance with literature data of the prevalence of the disease at a young age, under 30 years. In Table 2 the values of RDD, PDD, and Medication Adherence are reported by year of analysis. RDD values for Etanercept changed from a minimum of 5.81 mg/day in 2008 to a maximum of 6.87 mg/day in 2012. PDD was always higher than RDD and grew constantly from 2007 to 2012, from 6.67 mg/day in 2007 to 7.14 mg/day in 2012. The calculation of the medication adherence, as the ratio between RDD/PDD, varies from a minimum of 0.87 in 2008 to a maximum of 0.97 in 2009, describing a loss of adherence from 13% to 3%. RDD values for Adalimumab changed from a minimum of 2.29 mg/day in 2008 to a maximum of 2.60 mg/day in 2007. PDD values range from 2.78 mg/day in 2008 and 2.85 in 2011. Therefore, the values of medication adherence vary from a minimum of 0.83 in 2008 to a maximum

Table 1. Number of patients, age, sex, and sum of total days of treatment for Etanercept and Adalimumab.

	n					
	2007	2008	2009	2010	2011	2012
Etanercept						
n	12	22	25	20	23	21
Sex						
Male	1	1	2	1	3	4
Female	11	21	23	19	20	17
Age						
Median	46.5	51	53	54	56	54
Range	30–72	31–73	33–75	34–77	28–66	28–70
TDT						
Median	212	314.5	320	344	352	274
Range	118–293	29–365	125–365	70–365	90–365	149–361
Adalimumab						
n	9	18	27	29	23	10
Sex						
Male	0	2	3	3	3	3
Female	9	16	24	26	20	7
Age						
Median	54	53.5	55	53	53	58
Range	33–67	32–67	30–69	26–70	22–71	28–69
TDT						
Median	328	336	282	301	334	247
Range	146–353	66–365	54–365	29–365	113–365	126–332

Table 2. RDD, PDD, and medication adherence values from 2007–2012 for Etanercept and Adalimumab in the treatment of rheumatoid arthritis.

	2007	2008	2009	2010	2011	2012
Etanercept						
WRDD, Mean (SD)	5.90 (1.72)	5.81 (1.38)	6.30 (1.09)	6.36 (1.14)	6.32 (1.40)	6.87 (1.25)
WPDD, Mean (SD)	6.67 (1.15)	6.94 (0.92)	6.71 (1.23)	6.84 (1.14)	7.19 (0.25)	7.14 (0.00)
WADH, Mean (SD)	0.92 (0.33)	0.87 (0.28)	0.97 (0.25)	0.95 (0.28)	0.88 (0.20)	0.96 (0.18)
Adalimumab						
WRDD, Mean (SD)	2.60 (1.06)	2.29 (0.63)	2.50 (0.67)	2.55 (0.47)	2.58 (0.50)	2.48 (0.53)
WPDD, Mean (SD)	2.84 (0.06)	2.78 (0.14)	2.81 (0.08)	2.82 (0.08)	2.85 (0.04)	2.81 (0.08)
WADH, Mean (SD)	0.92 (0.37)	0.83 (0.23)	0.89 (0.25)	0.90 (0.16)	0.90 (0.17)	0.88 (0.17)

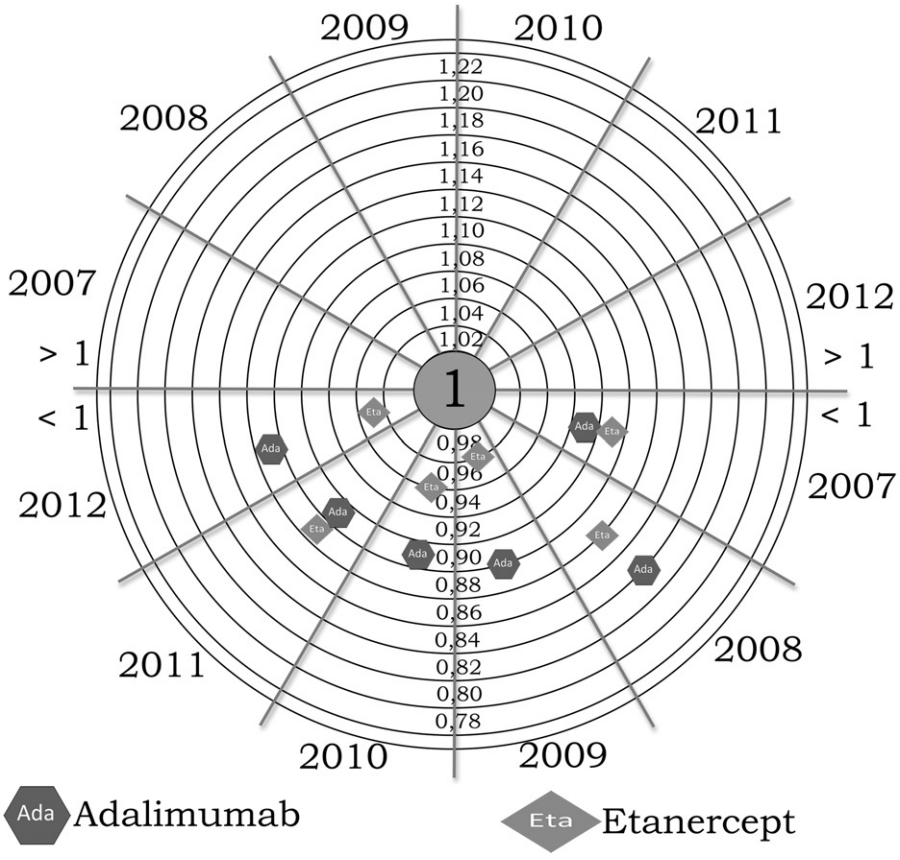

Figure 2. Values of adherence for Adalimumab and Etanercept from 2007–2012.

of 0.92 in 2007, describing a loss of adherence that varies from 12% to 8% (Figure 2). Persistence rate was represented with Kaplan Meier survival analysis and the results were identical among treatments with Etanercept and Adalimumab, and calculated Log-rank Test and χ^2 at 95% in the fourth year. The persistence to treatment was calculated from 1–4 years. In year 1 the rate of persistence (25 patients for Etanercept and 29 for Adalimumab) was 76% for Etanercept and 79% for Adalimumab; in year 2 (18 patients for Etanercept and 25 for Adalimumab) it was 61% for Etanercept and 60% for Adalimumab; in year 3 (16 patients for Etanercept and 20 for Adalimumab) it was 50% for Etanercept and 35% for Adalimumab; in year 4 (14 patients for Etanercept and 11 for Adalimumab) it was 21% for Etanercept and 27% for Adalimumab. The value of χ^2 in the fourth year was 0.29 at 95% of probability. This value, compared with table value, shows a complete overlapping of the two curves, and there is no significant difference (Figure 3). The cost per RDD for Etanercept was 31.06 €, 30.60 €, 33.20 €, 33.53 €, 33.31 €, and 36.17 €, while for Adalimumab it was 33.29 €, 29.34 €, 32.02 €, 32.61 €, 33.02 €, and 31.73 € from 2007–2012, respectively. The mean of real days of treatment was 302.75 for Etanercept and 304.66 for Adalimumab, the cost per patient per year was 9984 € for Etanercept and 9749 € for Adalimumab.

Discussion

Patient adherence has been defined by the World Health Organization (WHO) and by The International Society for Pharmacoeconomics and Outcomes Research (ISPOR), as the extent to which a person's behavior in taking medication corresponds to recommendations given by a healthcare provider and which that individual has agreed upon[20,21]. This definition explains effectively the intent of the study; in fact, as described above, medication adherence can be calculated efficiently by taking into account the intention-to-treat analysis of the physician and the behavior of the patient on the basis of the prescription. The use of purpose-built software, PharmaDDSS, allows users to record accurately the RDD and PDD, so as to calculate the medication adherence according to WHO's definition. The medication adherence is, therefore, calculated as the ratio between RDD/PDD and allows us to describe how the patient interprets therapy in relation to the suggestions of the doctor[22].

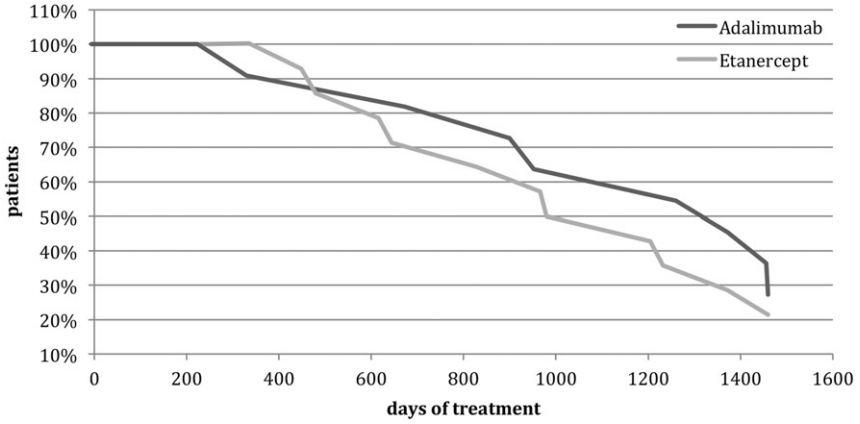

Figure 3. Persistence for Adalimumab and Etanercept in the treatment of rheumatoid arthritis.

The analysis of medication adherence showed a maximum loss of 12% for Etanercept and 13% for Adalimumab. This data shows that the patients who have used both Etanercept and Adalimumab took the doses recommended by physicians with considerable accuracy. A good adherence to drug treatment also shows a high tolerability of the drug which causes adverse events severe enough to require suspension in taking. The analysis of persistence shows good values in the first 2 years of treatment (75% in the first year, 60% in the second year). From the 3rd year, however, there was a significant increase in the levels of discontinuation of treatment, with a climax in the fourth year (50% for Etanercept, 65% for Adalimumab). This significant decrease in the level of medication persistence can be explained by patients' the difficulty in following the therapy for a long time. So, this data confirms the importance of carrying out surveillance programs in order to determine and document the efficacy and safety of TNF blocker in the long-term. It also confirms the need to quantify the percentage of switching and how the transition to another TNF inhibitor affects the clinical course. From a pharmacoeconomic point of view, the calculation of RDD can be useful in the study of budget impact of a drug based on real clinical practice. The calculation of RDD for each patient allows having a clear idea about the use of the drug and its use of economic resources allocated. In publication there are several examples showing the need for models of cost-effectiveness, based on the actual dose received by patients. In this way, it is possible to compare different drugs used for the same medical indication and, if the adherence and persistence overlap, it allows having a model for regulatory agencies to allocate resources[14,23–27]. In this retrospective analysis of 6 years, the average cost per patient per day of therapy, calculated on the basis of the doses actually taken by each patient, showed a substantial overlap between the two drugs. The annual cost per patient was €9984 for Etanercept and €9749 for Adalimumab.

Conclusion

The analysis of adherence and persistence for Etanercept and Adalimumab, conducted from 2007–2012, showed a contrasting result. Adherence to treatment was good during all years of analysis, while persistence showed a significant fall in the 4th year with 85% of patients who dropped out of therapy. This underscores the importance of distinguishing the concepts of adherence and persistence was distinct, although connected with one another. The same population of patients, in fact, may be adherent to treatment but not persistent or vice versa. In the case of biologics it is necessary to evaluate the impact of the switch from one TNF blocker to another by connecting the medication adherence and persistence to clinical outcomes, according to the formula: treatment – Adherence – Persistence – Outcomes. From the economic point of view the two drugs overlap with a treatment cost per patient per year (calculated as (Cost/RDD) × 365 days) for Etanercept vs Adalimumab of €11,680.00 and €12,000.00, respectively.

Transparency

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Declaration of financial/other relationships
The authors and CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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