Title Page

Does Etanercept biosimilar prescription in a rheumatology center bend the medication cost curve?

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Abstract

Objective: The market entry of biosimilars is expected to bring budgetary relief. Our objective was to determine how the introduction of biosimilars influences medication cost in patients with rheumatoid arthritis and which patients gain access to biologicals due to the availability of biosimilars.

Methods: Using hospital data of patients with rheumatoid arthritis between 2014 and 2018, an interrupted time series was performed. The interruption in the time series was placed at June 2016, i.e., the introduction of the etanercept biosimilar. The changes in trends for rheumatic medication cost before and after the interruption were measured. Secondary analyses focused on explaining these trends.

Results: In the first quarter after the interruption, there was a decrease in total cost for biologic users of €-63020 (CI=[€-96487;-€-29553]; P=0.001). The post-interruption trend did not differ from the pre-interruption trend (CI=[-€6695;€6715]; P=0.998) and after three quarters the medication cost were back at the interruption level. After the interruption, the average cost per biologic user decreased by €-370 (CI=[€-602;€-138]; P=0.005), followed by a quarterly decrease (relative to the pre-interruption trend) (CI=[€-86;€-14] P=0.010), bending the average cost curve. The percentage of patients being treated with biologics increased in post-interruption by 0.50 percentage points quarterly (CI=[0.38-0.62]; P<0.001). Also the average age at the start of the first biologic increased after the interruption (p=0.057).

Conclusions: The average cost per patient treated with biologicals decreased after the introduction of biosimilars with a persistent trend. However, the budgetary relief due to market entry of biosimilars vanished quickly due to an increase in patients treated with biologics.

1. Introduction

Cost containment in health care is a big issue in Western Countries. However, health care expenditures keep on growing. It is generally believed that when a patent on pharmaceuticals expires, this leads to a drop in health care cost. Whether and how this actually occurs in the Netherlands will be investigated in this paper. All expensive medication in the Netherlands is financed through the hospital, and costs are therefore part of Medical Specialist Care (MSC). However, at this point the growth of expensive medication cost exceeds the growth rate of the MSC as a whole. This means, given a fixed budget, that the expenditure on expensive medicines is displacing other care.(1)

Here the focus is on biologic medication of which the patent period has expired. It is anticipated that a decrease in prices for expensive medication, initiated through the availability of unpatented biologics, so called biosimilars, will lead to lower total costs and create budgetary relief.(1) Biosimilars are biotherapeutic products (biologics) that are similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product (bio-originator).(2) However, biosimilars have a significantly lower price and thereby induce price competition between bio-originator and biosimilar producers which is assumed to result in cost savings and finally bend the (total) cost curve.

These expectations, regarding the predicted budget impact of biosimilars, are based on many studies performed in the build-up to patent expiration of bio-originators.(3-8) All these studies predicted a cost saving. The amount of cost saving predicted differed, depending on the acquisition cost of the biosimilar drug,(8) the initial number of patients being treated with biologic therapy,(8) the number of biosimilars being available,(6) and the uptake of biosimilar use.(5)

One of the fields where the introduction of biosimilars is predicted to generate savings, is the treatment of rheumatoid arthritis (RA).(5, 6, 8) At this point, biosimilars for the TNF-Alfa blockers (a subgroup of biologics) adalimumab, etanercept and infliximab have been approved by the European Medicines Agency.(9) The expectations for biosimilars with regard to cost saving are high. For example, the chief executive of NHS recently announced that he expects the use of an adalimumab biosimilar to free up 300 million pounds (340 million euro) in the UK, which can be invested in patient care in general.(10) To assess the real-world impact of biosimilars, the impact of infliximab and etanercept biosimilars on the biologic disease-modifying antirheumatic drug (bDMARD) budget in the UK was studied.(11) The main finding of that study was that introduction of biosimilars indeed resulted in lower medication prices due to price reduction of both the bio-originators and the biosimilars. However, their data also showed an increase in the overall utilization of biologics, though they did not explain this finding further. Their data showed that this increased utilization of bDMARDs outweighed the price reduction achieved through the introduction of biosimilars. Therefore, no net savings were achieved even though prices for bDMARDs dropped.

Similar observations were made in the Netherlands, in a recent report based on real-world data from the Dutch Healthcare Authority (NZa). They observed a similar reduction in individual prices for existing expensive medication, accompanied with an increase in utilization of these expensive medications. Therefore the total cost for these medications increased.(1) For TNF-alfa blockers specifically they observed an increase of 11% in the volume of patients using bDMARDs.(1)

Both the NZa report(1) and the UK study(11) show an increase in the volume of bDMARDs for the treatment of RA. However, because these studies were based on national declaration data, they did not report on the mechanisms behind it nor did these studies report on which patients

gained access to bDMARDs. This evokes several questions from the perspective of a care provider. Is there a change in the percentage of patients using bDMARD therapy after the introduction of biosimilars? Are demographic and medical characteristics of patients receiving bDMARD treatment able to explain the potential change over time?

Our main aim was to study the impact of market entry of an etanercept biosimilar on medication cost in the biologic users of the RA population in a general hospital in the Netherlands. Secondary objectives were aimed at explaining the trends found.

2. Methods

Design

We studied the price effect of the introduction of biosimilars in RA using a single center interrupted time series design. The trends of total medication cost in bDMARD users and medication cost per patient using bDMARDs were compared before and after the introduction of an etanercept biosimilar at the Department of Rheumatology at Bernhoven in June 2016. Bernhoven is a medium-sized hospital in the south of the Netherlands that serves as a secondary referral centre in the region. This gives Bernhoven a case-mix of patients that is representative for general hospitals in the Netherlands.

From June 2016 onwards all patients who initiated etanercept treatment were treated with the biosimilar. The criteria for eligibility for bDMARD treatment in the Netherlands did not change during the study period: a Disease Activity Score 28 joints (DAS28) > 3.2 after treatment failure with at least 2 conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate in a dose of 25mg/week. (12) Since transitioning to a biosimilar is allowed in the Netherlands, all patients with inflammatory rheumatic diseases treated with the etanercept originator in Bernhoven were invited to transition to the biosimilar. About 87 percent

of these patients accepted the transition, with a one-year retention rate of 72 percent .(13) These rates fall well within the range observed by other studies in the Netherlands.(13)

During the study period an infliximab biosimilar became available at the hospital. However, as the prescription of infliximab for the treatment of RA is low in the Netherlands in general, only 10 patients received treatment with infliximab during the study period in Bernhoven , i.e. less than 4 percent of the DMARD users. Therefore, we deemed the influence of the introduction of the infliximab biosimilar negligible and focused on the introduction of the etanercept biosimilar.

Ethics

All patients gave their informed consent for use of their medical data for scientific purpose at an earlier point in time. Ethical approval was not necessary for this study, given the registry of common practice care based data collection.

Inclusion criteria

All patients with RA being treated at Bernhoven from June 1, 2014 up till June 1, 2018 were included in the analysis, providing a representative sample for the Dutch RA population. All patients included had been diagnosed with RA by their rheumatologist according to the ACR 2010 criteria.(14)

Data and instruments

Data on medication use of all patients with RA were collected using the electronic medical record system of Bernhoven. Information regarding the specific use of the etanercept bio-originator or the etanercept biosimilar was verified via the pharmacy of Bernhoven.

The following demographic and medical characteristics were collected: age, gender, rheumatoid factor (RF) positivity, anti-cyclic citrullinated peptides (anti-CCP) positivity, disease duration, disease activity. The DAS28 was used as a measure of disease activity (score between 0 and 10; higher score indicates higher disease activity).(15)

The quarters followed a 3 monthly sequence starting on the 1st of June 2014. For each quarter the sample consisted of all patients with an active diagnosis of RA at the department. Patients were categorised as bDMARD user if they were treated with a bDMARD during that quarter.

Rheumatic medication cost

Rheumatic medication cost (RMC) was defined as the cost for non-steroidal anti-inflammatory drugs, csDMARDs, bDMARDs, and glucocorticoids.

In the Netherlands bDMARDs are paid for through the hospital budget, and prices are negotiated with the pharmaceutical company per hospital. Therefore, information on the price of all bDMARDs was obtained from the pharmacy of Bernhoven to account for the negotiating bonus. These prices are confidential and therefore not disclosed here. During the study period the hospital negotiated a discount for the etanercept biosimilar.

Other medication, is directly reimbursed by health insurance companies. These prices are collected through the website www.medicijnkosten.nl as recommended by the Dutch guideline for cost-effectiveness research.(16)

Analyses

A single center interrupted time series analysis is used that estimates the coefficients by ordinary least squares regression with Newey–West standard errors to handle autocorrelation in addition to possible heteroscedasticity in the data. In general the regression model assumes the following form:

$$RMC_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \epsilon_t$$

RMCt is the aggregated rheumatic medication cost variable measured at each quarter *t* since June 1, 2014, *Tt* is the time since the start of the study, *Xt* is a dummy variable for the moment of interruption and *XtTt* is an interaction term. Of interest are β_2 *and* $\beta_3$which respectively show the

immediate price effect at time of interruption and the difference in trend between pre- and post-interruption. (17) Autocorrelation in the error distribution is tested by the Cumby–Huizinga general test for autocorrelation. Depending on the outcome of this test one or more lags are added to the model above. The interruption in the time series (quarterly intervals) was placed at June 1 ,2016, i.e., the drop in price due to the introduction of biosimilar(s). Time series were run to assess the RMC, first in the total RA population, then in bDMARD users only. Demographic and medical variables were added to the model to explain the trends found. The total RMC of the total RA population was adjusted for bDMARD cost to study the cost of the other rheumatic medication (i.e. csDMARDs and glucocorticoids). In a separate analyses, the average cost per patient in bDMARD users was adjusted for the bDMARD dosage, to assess whether bDMARD dosage influenced the average rheumatic medication cost per patient. The bDMARD dosage was standardized as percentage of the daily defined dosage.(18) An additional time series was run to assess the percentage of biological users, instead of the RMC, in the RA population over time. To take into account possible demographic differences between patients using bDMARDs in the pre-interruption and post-interruption period the RMC model(s) was run with the following covariates: BMI, age, and gender (adjusted model I). Similarly, it was investigated whether RA specific disease parameters differed between patients using bDMARDs in the pre- and post-interruption period including: RF positivity, anti-CCP positivity, age at diagnosis, age at start of first biologic and DAS28 at start of first biologic (adjusted model II). Analyses were done in STATA 15.1.

3. Results

Patients characteristics of the RA population

Between June 1, 2014 and June 1, 2018, the RA population in Bernhoven increased from 640 to 961 patients. The patient characteristics of the RA population and subgroup of bDMARD users at the 1st of June 2016 are shown in table 1. At that moment, 17 percent of the population was treated with bDMARDs. By June 2018, 20 percent of the population used a bDMARD and 28% percent of those were treated with the etanercept biosimilar.

Interrupted time series depicting the rheumatic medication cost in the total rheumatic arthritis population

The RMC of the total RA population in June 2014 was estimated at € 316521(CI=[29746;335796]; P<0.001) per quarter, and these cost appeared to increase significantly every quarter prior to June 2016 by € 19982 (CI = [15842;24121]; P<0.001). In the first quarter after the price drop due to the introduction of the etanercept biosimilar (June 2016), there appeared to be a significant decrease in RMC of € -63179 (CI=[-97638; 28718]; P=0.002). However the post-interruption cost trend did not change relatively to the pre trend (€212,CI=[-6629;7054]; P=0.947) and total costs were back to the level at the moment of interruption after three quarters. All absolute post-interruption trends are given in the supplementary data.

How heavily the RMC is influenced by the cost for bDMARDs, becomes apparent when studying respective influence of bDMARDs and of csDMARDs and glucocorticoids on the RMC. The RMC of the total RA population adjusted for bDMARD cost (giving the cost of csDMARDs and glucocorticoids) was estimated at € 10868 (CI=[4467;17269]; P=0.003). This means that the cost for bDMARDs accounted for around 96 percent of the total RMC. Interestingly, the average cost per patient for csDMARDs and glucocorticoids showed an increase over time. Since prices for these medication were assumed stable, this is an indication of intensifying treatment.

Interrupted time series depicting the rheumatic medication cost for biologic users

The total RMC of patients being treated with bDMARDs in June 2014 was estimated at € 301250 (CI = [282570;319930]; P<0.001), and these appeared to increase significantly every quarter prior to June 2016 by €19242 (CI = [15236;23248]; P<0.001). In the first quarter after the price drop, there appeared to be a significant decrease in total RMC of €-63020 (CI=[-96487;-29553]; P=0.001), whereas the quarterly post trend of total RMC (relative to the pre-price interruption trend) stayed more or less the same (€9, CI=[-6695;6715]; P=0.998) (see figure 1a).

The average RMC per patient being treated with bDMARDs in June 2014 was estimated at € 2869 (CI=[2727;3011]; P<0.001) per quarter, and these appeared to increase significantly every quarter prior to the 2nd quarter of 2016 by €31 (CI = [2;61]; P=0.041). In the first quarter after the price decrease, there appeared to be a significant decrease in average RMC per patient of € -370 (CI=[-602;-138]; P=0.005), followed by *a significant decrease* in the quarterly trend of the average RMC per patient (relative to the pre-price interruption trend) of €-50.34 per quarter (CI=[-86;-14]; P=0.010) (figure 1b). Contrary to the total RMC curve, the average RMC curve for biologic users bends downward after the drop in price, implying that average cost per patient using bDMARDs decreased further over time. Adjustment for the bDMARD dosage as percentage of the daily defined doses, did not alter the average RMC per patient (€-682,CI=[-4860;3497]; P=0.726). This means that there was no effect of dose intensity on the average cost per patient for biologic rheumatic medication.

This seeming paradox that the curve for total RMC in bDMARD users does not bend while the average cost per bDMARD user drops can be explained by looking at the number of biological users in total RA population. There was a significant increase (0.22 percent, CI = [0.11-0.32]; P=0.001) per quarter in percentage of patients being treated with bDMARDs prior to the introduction of biosimilars (figure 1c). This trend significantly increased further after the introduction of the etanercept biosimilar (0.28 percent CI = [0.10-0.47]; P=0.006) leading to a

significant post trend increase per quarter (0.50 percent, CI = [0.3791;0.6204]; P<0.001) (figure 1c). This increase in patients being treated with bDMARDs counterbalances the individual price reduction achieved by biosimilars.

Can trends in cost be explained by demographics or diseases specific parameters of biologic users over time

Table 2 shows the patients' characteristics and medication use of patients initiating their first biological treatment before and after the introduction of the etanercept biosimilar. After the introduction of the biosimilar, patients tend to be older at the initiation of their first bDMARD and use less csDMARDs as co-medication. To study the influence of changes in patient characteristics two adjusted models, mentioned in the method section, were run. Both the inclusion of the demographic variables (adjusted model I) and inclusion of the RA disease specific parameters (adjusted model II) could not explain the cost results in a significant way (supplementary data). However, the variable patients' age at start of first biologic was near significant (p=0.057), meaning that bDMARD users in the post-interruption period were increasingly older.

4. DISCUSSION

This study observes the bending of the average medication cost curve for patients being treated with a bDMARD when an etanercept biosimilar becomes available. However, we notice that the trend in the total cost curve stays the same, i.e., no sustainable free disposable savings could be collected. This occurs because price reduction achieved by the introduction of the biosimilar facilitates an increase in bDMARD users, which counteracts the initial cost saving.

This study was applied in a real-world setting. A strength of this approach is that the data provide the opportunity to study which patients gained access to bDMARDs. Next to that, the interrupted time series design has the capability of identifying underlying trends, thereby isolating the effect

of the introduction of biosimilars on the trend. This increases the confidence with which observed effects can be attributed to the introduction of biosimilars. A limitation is that data from only one hospital were obtained for analysis. However, Bernhoven is a typical Dutch referral center, with a case-mix of patients that is representative for general hospitals in the Netherlands when it comes to its RA population. We verified this by comparing our population with the RA population from the DREAM consortium, a collaboration between 13 hospitals in the Netherlands. Our RA population and the subgroup of bDMARD users were comparable on age, gender, disease duration and rheumatic antibody levels. (19) Findings regarding increased utilization were also in line with other (nationwide) real-world data, further strengthening our conclusions.(1, 11)

After the initial price reduction achieved through the market entry of the etanercept biosimilar, we observed a bending in average medication cost curve for bDMARD users. This means that the average treatment cost per patient for bDMARD users decreased over time after the availability of the etanercept biosimilar. This correspondents to the gradual increase in uptake of the etanercept biosimilar, driving down the cost. At the same time, the total medication cost curve did not change, because the potential savings, achieved through biosimilar use, were used to further increase prescription to bDMARDs. These findings are similar to the NZa report, which shows that across different indications, the volume of patients using expensive medication increases, while the budget remains more or less stable. (1)

In Bernhoven the additional increase in bDMARD prescription after the introduction of the biosimilar, happened unconsciously and autonomously. The rheumatologists had not consciously changed their prescription policy, and only became aware of the increase in bDMARD prescription after the conducting of this research. The question arises whether this automatic return of savings to RA care, where it funds an increase in bDMARD prescription is desirable. Where current literature only focuses on national declaration data lacking patient specific

demographic and medical data, (1, 11) our data offers the possibility to assess which patients gained access to bDMARD therapy. It is known that older patients are less likely to receive biologic treatment.(20, 21) The observed increasing prescription of bDMARDs could be a response to previously undertreatment in that group. The interrupted time series (adjustment model II) shows that bDMARD users tend to be older after the introduction of biosimilars, supporting this hypothesis. The adjustment models were unable to detect other differences between the pre and post-interruption group. This was perhaps due to insufficient power, to detect differences on group level. When focusing on patient initiating bDMARD therapy, we observed that after the introduction of the biosimilar, patients use less csDMARD co-medication at the initiation of bDMARD therapy. The percentage of patients using methotrexate as co-medication dropped from 68 to 54 percent. This could be an indication that patients were given the chance, by initiating a bDMARD, to stop their csDMARD with adverse-effects.

The actual health benefits of additional bDMARD prescription remain very difficult to assess. On population level, there was no change in disease activity during the study period, but we observed a small non-significant improvement in disability (data not shown here). However, in absolute numbers there was only a small increase in bDMARD users, i.e. 4 percent. Therefore possible effects are diluted on population level and difficult to assess. In relative numbers there was an increase of nearly 25 percent in the number of bDMARD users. A change in the type of patients receiving a bDMARD therapy comes with the risk that the treatment is less effective in the new target population.(22, 23) Expansion of bDMARD therapy to older patients might affect the cost-benefit ratio of bDMARDs therapy, and should be further examined. That increased access to bDMARDs might not be the best investment from a societal perspective is shown by a recent study which shows that reinvesting biosimilar savings in RA care came only at the fifth place

regarding cost-effectiveness if quality of life maximization is feasible, in a country where patients have readily access to bDMARDs.(22)

At this point, the general opinion is that biosimilars have the potential to generate billions of euros in savings in Europe alone,(24) and that payers are likely to experience some relief of budgetary constraints or the ability to reallocate funds, depending on the policy priorities of each country.(22) Already biosimilars help reduce access inequities and lead to an increase in bDMARD prescription in Europe. (25) We found that the total medication cost before and after the introduction of biosimilars remained more or less the same, while the number of bDMARD users increased. Therefore, the assumption that the availability of biosimilars facilitates increased access to biologic therapy in Europe seems valid.(24) However, the discrepancy between expected and realized budgetary saving is significant. Our study and other available data regarding real-world savings show that no net savings were achieved by biosimilar use, because freed up funds were used for increasing access to biologic therapy within the same indication.(1, 11) This phenomenon, that a price decrease leads to an increase in volume of patients treated, which is well known in economics, is often overlooked and seldom anticipated in real world policy-making.(26) Further research should focus on the cost-effectiveness of expanding access to bDMARD therapy.

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figure 1a: total medication cost of patients being treated with bDMARDs from June 1, 2014 up till June 1, 2018

figure 1b: average cost per patients being treated with bDMARDs from June 1, 2014 up till June 1, 2018

figure 1c: the percentage of patient, who are bDMARD users from June 1, 2014 up till June 1, 2018

Table 1 Patient characteristics of the total population and the subgroup of patients using biologic disease modifying anti-rheumatic drug in June 2016

Characteristics	RA population		bDMARD users	
	827	N	141	N
Patient characteristics				
Age in years, mean (SD)	63(14)	827	58(14)	141
Disease duration in years, mean (SD)	8(8)	824	11(9)	141
Female gender, %	65	541	70	99
DAS28, mean (SD)	3.1(1.2)	630	3.3	3.3(1.5)
RF positive, %	57	392	56	69
Anti-CCP positive, %	55	378	63	78
BMI, mean (SD)	27(10)	432	26(5)	58

RA= Rheumatoid arthritis; bDMARD= Biologic disease modifying anti-rheumatic drug; DAS28= Disease Activity Score 28-joints; RF=Rheumatoid Factor; Anti-ccp= anti-cyclic citrullinated peptides; BMI=Body Mass Index; SD= standard deviation.

Patient characteristics	Before introduction of biosimilar		After introduction of biosimilar	
	59	N	67	N
Baseline characteristics				
Mean (SD) age at start biological, years	52(14)	59	58(14)	67
Mean (SD) disease duration at start biological, years	4(6)	59	4(6)	67
Female gender, %	74.6	44	70.1	47
RF positive, %	42.3	22	56.4	22
Anti-CCP positive, %	51.9	27	55.6	25
Mean (SD) BMI	27.0(7)	40	27.8(7)	35
Mean (SD) DAS28 at start biological	4.7(1.3)	38	4.5(1.2)	42
Medication use prior to initiation of first bDMARD				
Mean (SD) number of csDMARDs used	2.1(0.7)	57	2.1(0.7)	60
Patients with glucocorticoid treatment in last year, %	73	43	73	49
Mean (SD) number of prednisone prescription in last year	2.7(2.5)	59	2.6(2.6)	67
Medication use during initiation of first bDMARD				
Distribution of bDMARD utilisation at initiation of first bDMARD				
Abatacept	-	-	2	1
Adalimumab	53	31	42	28
Etanercept	36	21	46	31
Certolizumab	-	-	3	2
Golimumab	3	2	2	1
Infliximab	2	1	-	-
Rituximab	5	3	3	2
Tocilizumab	2	1	3	2
Number of csDMARD at start of biological (co-medication)				
0	14	8	27	18
1	44	26	37	25
2	42	25	35	24
Patients using MTX at start of biological, %	68	40	54	36

Table 2 Patient characteristics and medication use of people starting biologic treatment in the years 2015 and 2017. RF=Rheumatoid Factor; Anti-ccp= anti-cyclic citrullinated peptides; BMI=Body Mass Index; DAS28=Disease Activity Score 28 joint count; csDMARD= conventional synthetic Disease-Modifying Anti Rheumatic Drugs; MTX=methotrexate.

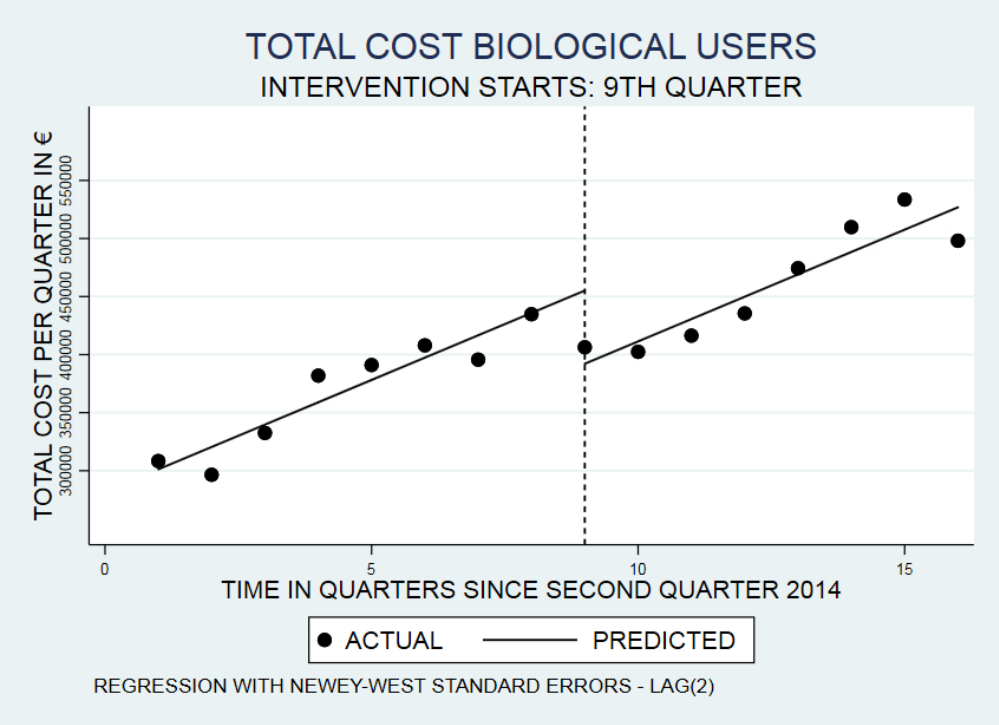

Figure 1a: total medication cost of patients being treated with bDMARDs from June 1, 2014 up till June 1, 2018

298x217mm (72 x 72 DPI)

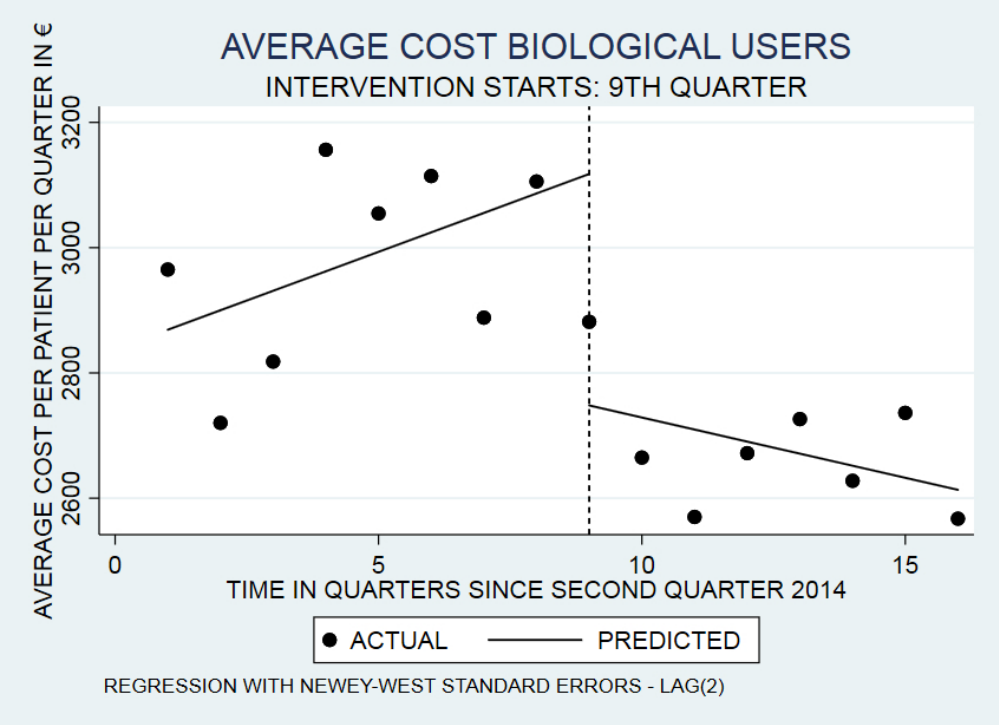

Figure 1b: average cost per patients being treated with bDMARDs from June 1, 2014 up till June 1, 2018

298x217mm (72 x 72 DPI)

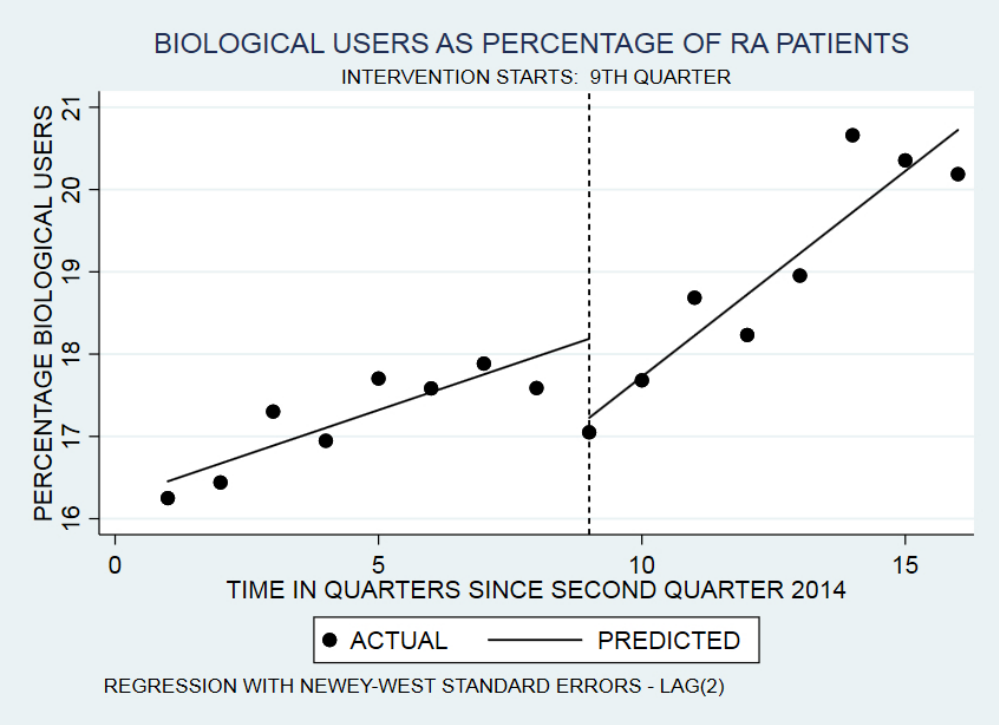

Figure 1c: the percentage of patient, who are bDMARD users from June 1, 2014 up till June 1, 2018

298x217mm (72 x 72 DPI)

Supplementary table 1: absolute post-interruption trends.

	Post-interruption trend coefficient	Newey-West standard error	P-value	95% confidence interval	
RMC of total RA population	20200	2789.98	0.0000	14100	26300
RMC of total RA population adjusted for bDMARD cost	661	170.6739	0.0026	285.48	1036.78
RMC of patients being treated with bDMARD's	19300	2748.71	0.0000	13300	25200
Average RMC per patient being treated with bDMARDs	-19.25	12.5827	0.1521	-46.6611	8.1696
Percentage of patients being treated with bDMARDs	0.4997	0.0704	0.000	0.3463	0.6532

RMC= Rheumatic Medication Cost; RA Rheumatoid Arthritis; bDMRADs= biologic Disease-Modifying Anti Rheumatic Drugs.

Supplementary table 2: Adjusted model I. Average cost biological users adjusted for BMI, Age and Gender.

	coefficient	Newey-West standard error	P-value	95% confidence interval	
Estimate	-4095,33	23297,05	0,864	-56797,36	48606,7
pre-interruption trend	28,76	44,02	0,530	-70,81	128,35
post-interruption trend	398,94	149,42	0,026	-736,94	-60,94
Interruption	-107,9	102,37	0,319	-339,48	123,68
Body Mass Index	-366,28	507,81	0,489	-1515,03	782,47
Age, years	286,14	507,64	0,587	-862,21	1434,51
Gender, women	-16,04	83,57	0,852	-205,09	173,01

Supplementary table 3: Adjusted model II. Average cost biological users adjusted for rheumatic factor, anti-ccp and Gender.

	coefficient	Newey-West standard error	P-value	95% confidence interval	
Estimate	14357,37	5413,01	0,029	1874,95	26839,79
pre-interruption trend	14,21	61,58	0,823	-127,78	156,21
Relative post-interruption trend	-440,29	122,39	0,007	-722,51	-158,07
Interruption	31,42	86,93	0,727	-169,04	231,88
Rheumatic factor positive	-21,61	30,44	0,498	-91,8	48,59
Anti-ccp positive	-52,19	42,86	0,258	-151,02	46,63
Age at initiating first bDMARD	-109,15	53,09	0,074	-231,57	13,27
DAS28 at initiating first bDMARD	-220,32	493,63	0,667	-1358,64	917,99

Anti-ccp= anti-cyclic citrullinated peptides; DAS28=Disease Activity Score 28 joint count; bDMARD= biologic Disease-Modifying Anti Rheumatic Drugs.