# Treat-to-target biologic therapy in patients with rheumatoid arthritis is more efficacious and safe compared to delayed initiation of biologics: a real-world study

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## Abstract

### Objective

*Rheumatoid arthritis (RA) is a chronic, devastating disease. Treat-to-target strategy (T2T) more than the usual care, reduces disease activity by using aggressively all therapeutic options. The aim of the study was to evaluate our hypothesis that T2T strategy using biologic disease-modifying anti-rheumatic drugs (bDMARDs), when needed, is also safer than the usual care characterised by delayed initiation of bDMARDs.*

### Methods

*Disease activity was regularly measured by DAS-28 until the end of treatment with the first bDMARD. All adverse events (AEs) and their severity were recorded. Cox proportional-hazards models were performed examining the association of treatment groups, with the risk of first AE.*

### Results

*There were 113 patients in T2T and 250 patients in usual care group. The likelihood (adjusted hazard ratio, HR) of achieving remission or LDA was 71% higher in the T2T group than in the usual care group, as it has been already shown by others. The novel finding of our work was that AEs, including cancers, were less frequent in the T2T group with the corresponding HRs being less than 0.50 for serious AEs, infections and serious infections (significant or marginally non-significant results). There were 15 new cancer cases in usual care and 1 in T2T group (IR 1.99 vs. 0.4, p=0.027).*

### Conclusion

*Treat-to-target treatment with bDMARDs offers a safer, rapid and better long-term outcome to patients with RA.*

**Key words**

rheumatoid arthritis, treat-to-target therapy, biologic treatment, adverse events, infections

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## Introduction

Rheumatoid arthritis (RA) is an autoimmune disease with joint destruction, resulting in functional impairment and permanent disability in these patients. It has been proved that joint destruction appears early in disease course, while rapid deterioration during the first year is a significant predictor for further progression (1). During the last decade, great advance has been made in patients' quality of life, after addition of newer targeted therapies. European League Against Rheumatism (EULAR) recommended a treat-to-target strategy (T2T) with proper initiation of all possible treatment options, in order to aggressively reduce joint inflammation and improve outcome (2, 3). Since then, many trials have shown that T2T therapy rapidly induces remission, significantly improves quality of life and that it is cost-effective compared with usual care (4-6).

Although these recommendations were accepted worldwide as the ideal treatment approach, there were not feasible enough during routine care of RA patients in an outpatient clinic (7). Lack of compliance is noticed in these patients as the frequency of visits is not as strict as in randomised studies; patient population is more heterogeneous with many co-morbidities that may affect therapy options; validated measures of disease activity are not always used in outpatient clinics; and finally, judgment of physicians or even patients on treatment options or decisions is always an imponderable factor (8). It has also been shown that only a minority of patients in routine care could participate in prospective trials, because of their strict inclusion criteria requirements (9).

Apart from efficacy, not much attention was paid to side effects occurring after T2T therapy as compared to the usual care. Our hypothesis was that T2T therapeutic strategies including biologic disease-modifying anti-rheumatic drugs (bDMARDs), when required, are associated with better safety profiles than usual care strategies. Thus the objective of this real-world, observational study was to estimate whether prompt initiation of bDMARDs, according to EULAR therapeutic algorithm, in patients with RA, apart from the efficacy, offers a better safety profile as compared to usual care. We defined as usual care the initiation of biologic treatment, 12 months or more after residual disease activity was noted, or more than 6 months after a relapse.

## Materials and methods

*Study population*

The files of 1403 patients (295 men and 1108 women) with RA, diagnosed according to American College of Rheumatology classification criteria and followed in our department, were retrospectively evaluated. Among those, 375 patients have received their first bDMARD, for at least 3 months, in our department, following failure of previously administered methotrexate (MTX) or any other synthetic DMARD (sDMARD). After excluding those younger than 18 years, those followed-up less than 3 months or those receiving only steroids, 363, biologic-naïve, individuals included in the analysis, of whom 113 were treated according to T2T strategy and 250 in the context of usual care. All patients were evaluated for latent or active tuberculosis according to international guidelines and treated appropriately (10). The study protocol was approved by the Ethics Committee of our university hospital and is consistent with the principles of Helsinki declaration.

*Study outcome*

Efficacy of treatment was determined according to EULAR response criteria: low disease activity (LDA) was defined as Disease Activity Score-28 (DAS-28) ≤3.2 and a DAS-28 reduction of more than 1.2 compared to initial DAS-28; remission as a DAS-28 ≤2.6 together with the aforementioned reduction; moderate disease activity (MDA) when the criteria for LDA or high disease activity (HDA) were not fulfilled, and HDA when treatment failure (alteration of DAS-28 <0.6 or final DAS-28 >5.1 with alteration less than 1.2) was noticed (11). Achieving a remission or LDA was considered as a good response to treatment.

Severity of AEs was classified according to the Common Terminology

Criteria for Adverse Events (CTCAE, version 4.03, 2010, U.S. Department of Health and Human Services), which is a 5 grade severity system as follows: 1=mild (asymptomatic or mild symptoms, clinical or diagnostic observation only, intervention not indicated), 2=moderate (minimal, local or non-invasive intervention indicated), 3=severe but not immediately life-threatening (hospitalisation indicated), 4=life-threatening consequences (urgent intervention indicated), 5=death. Grades 1 and 2 are considered as mild, not necessitating admission in hospital, while grades 3–5 are considered as serious. The outcome studied was either the first AE (in total) or the first infection (mild or serious) encountered during follow-up within the Unit. If a patient had multiple outcomes during follow-up, he/she was counted only once in the survival analysis. A separate analysis was performed for new cases of cancer presented during administration of bDMARDs.

*Treatment groups*

Patients were separated into 2 groups: T2T group included patients with bDMARD administration, after initial treatment failure (DAS-28 >3.2), according to EULAR recommendations: early initiation of bDMARD after 3-6 months of treatment with parallel existence of unfavourable prognostic factors [HDA, early radiographic damage, high rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA) titers] or after 6-12 months of appropriate titration of sDMARDs, in absence of the aforementioned risk factors. Patients, who had initially achieved remission or LDA with sDMARDs and received a bDMARD with their first flare-up, were included in this group. The second group consisted of patients with initiation of bDMARD after more than 12 months despite active joint inflammation, or patients treated with a bDMARD after more than 6 months following a disease flare (usual care group).

*Assessment of covariates*

Baseline information was collected for all patients with regard to demographic and disease related data. The following baseline data were used in the analyses, all introduced as categorical variables except for: sex (men, women), age which was used continuously per year, bDMARD (infliximab, adalimumab, etanercept, other), initial DAS-28 (3 variables) for first bDMARD provided (categorically, >5.1, 3.2 to 5.1, 2.6 to 3.2, ≤2.6), incident case (yes, no), early treatment (≤3, 4-12, ≥13 months after the first disease-related symptoms), extra-articular manifestations (no, yes), erythrocyte sedimentation rate (ESR, <40mm/h, ≥40 mm/h), swollen joint count (SJC) for first bDMARD (<5, 6–10, ≥11), type of joints (small, large, both), steroid total dose (<500 mg, >500 mg, none), smoking status (never, former, current) and co-morbidities at first treatment initiation (no, yes, plus an unknown/missing category since there were individuals without information on co-morbidities). Co-morbidities included cardiovascular disease (CVD), cancer, metabolic disease (diabetes mellitus, dyslipidaemia, obesity), lung disease, gastrointestinal and liver disease, tuberculosis, viral hepatitis, neuropsychiatric disease, renal and thyroid disease. Disease activity was measured at initiation of bDMARD, after 3, 6 and 12 months and then annually until the end of the first bDMARD.

Finally, as potential risk factors for cancer appearance, there were recorded the following parameters: smoking habits, previous radiation, transplantation and relevant medicine, toxic drugs, professional occupation, family history and/or interstitial lung disease.

*Statistical analysis*

For descriptive purposes, study characteristics are presented as frequencies and percentages except for age (mean +SD), by treatment group and by efficacy of treatment. A *t*-test for mean age difference and Chi-square tests for the categorical variables were applied.

Incident rates (IR) of the first total or serious AE (CTCAE score 3–5) and the first total or serious infection, as well as the corresponding incidence rate ratios (IRRs), were estimated based on the person-years (PY) contributed by patients, for the period from the initiation of the bDMARD up until the time which the first AE or infection occurred.

Kaplan-Meier (KM) plots with logrank tests were applied and subsequent multivariate Cox proportional-hazards analyses were performed in order to assess the association of the treatment group with the likelihood (hazard ratio, HR) of achieving remission or LDA overall and by specific bDMARD, as well as with the risk of first AE or infection, after adjusting for the aforementioned potential confounders. If an AE occurred after the patient had discontinued a bDMARD, that event was not included in the analysis. In the former case, achievement of remission or LDA was the event and the time to this event was used in the survival analysis, while in the latter case, the occurrence of an AE was defined as the event and the time until the first such event was used in the corresponding survival analyses. The proportional hazards assumption was evaluated through the use of time-varying covariates.

Data were analysed using STATA (Stata/SE 11.0. for Windows; Stata Corporation, College Station, TX, USA).

## Results

*Patient characteristics*

There were 113 patients in T2T group and 250 patients in the usual care group. Study-sample characteristics for all patients are presented in Table I. The proportion of men treated with T2T was almost twofold the corresponding percentage of women. The proportion of individuals in the T2T group appears to vary across categories of the baseline variables.

*Efficacy of treatment*

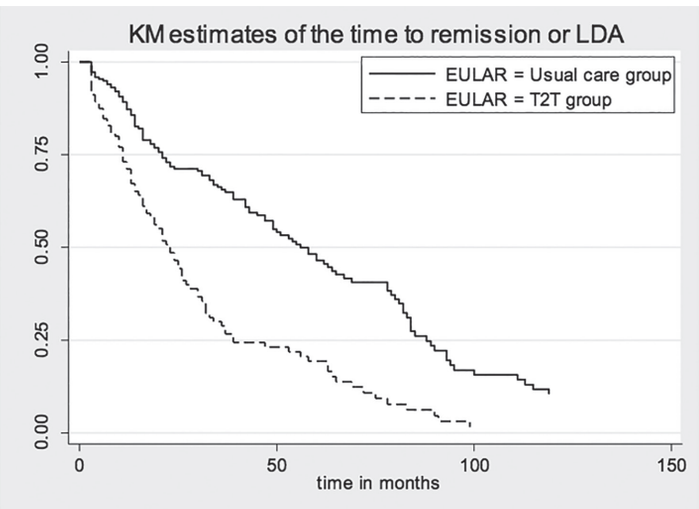
After 3 months of treatment, 65 patients (58%) from T2T group achieved remission or LDA (43 and 22 respectively) compared to 103 patients (41%) of the usual care group (76 and 27 respectively). After 12 months, in T2T group there were 53/83 patients (64%) with remission and 14/83 (17%) with LDA (in total 81% with good response) compared to 74/188 patients (39%) and 42/188 (22%) respectively in the usual care group (61% with good response). After 24 months, in T2T group there

**Table I.** General characteristics of 363 patients with RA treated with bDMARDs by time of institution (EULAR recommendations) and by efficacy of treatment (EULAR response criteria).

| | Treatment strategy | | | | | Efficacy of treatment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Usual care group | | T2T group | | | No | | Remission/LDA | | |
| | 250 | | 113 | | | 141 | | 222 | | |
| | M | SD | M | SD | *p* | M | SD | M | SD | *p* |
| Age in years | 53 | 14 | 53 | 14 | 0.949 | 55 | 13 | 51 | 15 | **0.008** |
| | **n.** | **%** | **n.** | **%** | | **n.** | **%** | **n.** | **%** | |
| Sex | | | | | **<0.001** | | | | | 0.373 |
| Men | 44 | 52 | 41 | 48 | | 29 | 34 | 56 | 66 | |
| Women | 206 | 74 | 72 | 26 | | 112 | 40 | 166 | 60 | |
| Biologic agent | | | | | **<0.001** | | | | | **0.001** |
| *Infliximab* | 99 | 83 | 20 | 17 | | 63 | 53 | 56 | 47 | |
| *Adalimumab* | 65 | 75 | 22 | 25 | | 32 | 37 | 55 | 63 | |
| *Etanercept* | 61 | 52 | 56 | 48 | | 34 | 29 | 83 | 71 | |
| *Other* | 25 | 62 | 15 | 38 | | 12 | 30 | 28 | 70 | |
| **Treatment therapy** | | | | | | | | | | **<0.001** |
| ***Usual care*** | | Not applicable | | | | 120 | 48 | 130 | 52 | |
| ***T2T*** | | | | | | 21 | 19 | 92 | 81 | |
| Incidence case | | | | | **<0.001** | | | | | 0.385 |
| No | 176 | 86 | 29 | 14 | | 84 | 41 | 121 | 59 | |
| Yes | 74 | 47 | 84 | 53 | | 57 | 36 | 101 | 64 | |
| Early treatment (in months) | | | | | **<0.001** | | | | | 0.206 |
| ≤3 | 67 | 57 | 50 | 43 | | 45 | 38 | 72 | 62 | |
| 4 to 12 | 84 | 67 | 41 | 44 | | 42 | 34 | 83 | 66 | |
| 13+ | 99 | 82 | 22 | 18 | | 54 | 45 | 67 | 55 | |
| Swollen joints | | | | | **0.008** | | | | | *0.070* |
| ≤5 | 147 | 65 | 80 | 35 | | 78 | 34 | 149 | 66 | |
| 6 to 10 | 88 | 80 | 22 | 20 | | 50 | 45 | 60 | 55 | |
| 11+ | 15 | 58 | 11 | 42 | | 13 | 50 | 13 | 50 | |
| Type of joints | | | | | **<0.001** | | | | | **0.002** |
| Small | 15 | 42 | 21 | 58 | | 5 | 14 | 31 | 86 | |
| Large | 22 | 48 | 24 | 52 | | 15 | 33 | 31 | 67 | |
| Both | 213 | 76 | 68 | 24 | | 121 | 43 | 160 | 57 | |
| Extra-articular manifestations | | | | | **<0.001** | | | | | *0.055* |
| No | 61 | 49 | 64 | 51 | | 40 | 32 | 85 | 68 | |
| Yes | 189 | 79 | 49 | 21 | | 101 | 42 | 137 | 58 | |
| ESR (in mm/hour) | | | | | 0.495 | | | | | **0.002** |
| <40 | 139 | 71 | 58 | 29 | | 62 | 31 | 135 | 69 | |
| 40+ | 111 | 67 | 55 | 33 | | 79 | 48 | 87 | 52 | |
| Initial DAS-28 from 1st biol | | | | | 0.627 | | | | | **0.002** |
| >5.1 | 117 | 71 | 48 | 29 | | 77 | 47 | 88 | 53 | |
| >3.2 to 5.1 | 122 | 68 | 57 | 32 | | 54 | 30 | 125 | 70 | |
| >2.6 to 3.2 | 7 | 54 | 6 | 46 | | 5 | 38 | 8 | 62 | |
| ≤2.6 | 4 | 67 | 2 | 33 | | 5 | 83 | 1 | 17 | |
| Steroid total dose (mg) | | | | | **<0.001** | | | | | **<0.001** |
| <500 | 163 | 67 | 82 | 33 | | 91 | 37 | 154 | 63 | |
| >500 | 66 | 96 | 3 | 4 | | 41 | 59 | 28 | 41 | |
| None | 21 | 43 | 28 | 57 | | 9 | 18 | 40 | 82 | |
| Smoking status | | | | 0.418 | | | | | 0.327 | |
| Never | 187 | 68 | 87 | 32 | | 101 | 37 | 173 | 63 | |
| Former | 6 | 55 | 5 | 45 | | 4 | 36 | 7 | 64 | |
| Current | 57 | 73 | 21 | 27 | | 36 | 46 | 42 | 54 | |
| Co-morbidities | | | | | **0.006** | | | | | |
| No | 119 | 68 | 56 | 32 | | 59 | 34 | 116 | 66 | |
| Yes | 98 | 64 | 54 | 36 | | 62 | 41 | 90 | 59 | |
| Unknown* | 33 | 92 | 3 | 8 | | 20 | 56 | 16 | 44 | |

*An unknown/missing category was included for the co-morbidities variable. T2T: treat-to-target. Mean differences in age were assessed through t-test while the association of categorical variables was assessed by the Chi-square test.

were 33/56 patients (59%) with remission and 14/56 (25%) with LDA (in total 84% with good response) compared to 63/146 patients (43%) and 34/146 (23%) respectively of the second group (66% with good response). Regarding the T2T group, after 3 years of continuous administration of the first bDMARD, there were 24/33 patients (73%) with remission and 6/33 (18%) with LDA compared to 49/115 patients (43%) and 26/115 (23%) respectively of the second group (good response in 91% and 66% respectively). At the last follow-up of first bDMARD treatment




**p-value <0.001**

**Fig. 1.** Kaplan-Meier plot depicting the fraction of patients who achieved remission or LDA after treatment initiation with the first bDMARD.

in T2T group, 61 patients (54%) had remission, 31 (27%) LDA, 8 (7%) MDA and 13 (12%) remained with HDA. On the contrary, in the usual care group 81 patients (32%) achieved remission, 49 (20%) LDA, 54 (22%) MDA and 66 (26%) remained with HDA. Comparison between the two groups revealed a statistically significant advantage of the T2T strategy in terms of remission and/or LDA (*p*<0.001). The IR for T2T group was 37.16 (95% CI 30.29-45.58) and for usual care group 17.26 (95% CI 14.54–20.50). The IRR between the 2 groups was 2.15.

The KM plots (Fig. 1) depicted that the likelihood for a good response was significantly higher among patients of the T2T group (*p* of logrank test <0.001). This advantage was independent of the type of the anti-tumour necrosis factor-α (anti-TNF-α) inhibitors: infliximab (*p*=0.008), adalimumab (*p*=0.018) and etanercept (p<0.001) were comparably effective (Fig. 2). The mutually adjusted HR of the likelihood of achieving remission or LDA was 1.71 (95% CI 1.18-2.47, *p*=0.004) in favour of those belonging to the T2T group after controlling for all the aforementioned confounders, except co-morbidities which had several missing data (Table II). When the latter was further introduced in the model, the change in the HR was negligible.

As it regards to the effect of other con-

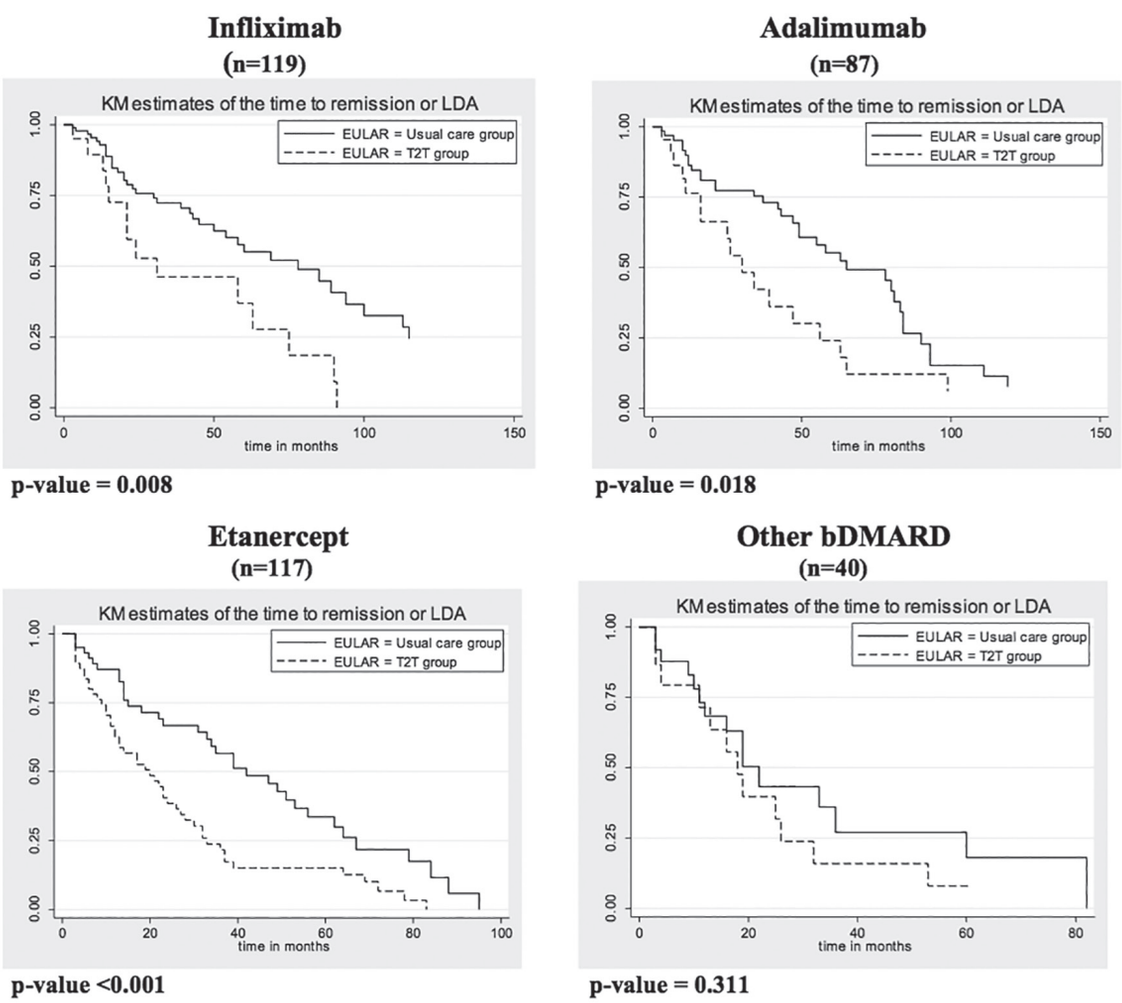



**Fig. 2.** Kaplan-Meier plots depicting the fraction of patients who achieved remission or LDA after treatment initiation with the first specific bDMARD.

**Table II.** Mutually adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) of the risk of remission or LDA (primary endpoint) or the risk of the first AE or infection (minor or serious) (secondary endpoints) by EULAR criteria (usual care *vs*. T2T group).

| n=363 | Primary endpoint | | Secondary endpoints | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Remission / LDA (222 events) | | Adverse event (202 events) | | Serious adverse event (65 events) | | Infection (91 events) | | Serious infection (32 events) | |
| | HR | P | HR | P | HR | P | HR | P | HR | P |
| EULAR protocol | | | | | | | | | | |
| Usual care group | ref | | ref | | ref | | ref | | ref | |
| T2T group | 1.71 | **0.004** | 0.78 | 0.263 | 0.42 | **0.041** | 0.49 | *0.052* | 0.24 | *0.065* |

T2T: treat-to-target. *After controlling for the following potential confounders: sex (men, women); age (continuously per year); bDMARD (categorically, infiximab, adalimumab, etanercept, other); initial DAS-28 for first bDMARD provided (categorically, >5.1, >3.2 to 5.1, >2.6 to 3.2; ≤2.6); incident case (no, yes); early treatment (categorically, ≤3 months, 4 to 12 months, 13+ months); extra-articular manifestations (no, yes); SJC for first bDMARD (categorically, ≤5, 6-10, 11+); type of joints (categorically, small, large, both); ESR (<40 mm/hour, 40+ mm/hour); steroid total dose (categorically, <500mg, ≥500mg, none) and smoking status (categorically, never, former, current).

**Table III.** Rates of AEs by treatment group, according to EULAR T2T treatment recommendations.

| n. | Usual care group 250 | T2T group 113 |
|---|---|---|
| | First AE (overall) | |
| PY for first AE | 480 | 187 |
| n.. of AE | 155 | 47 |
| IR | 32.29 | 25.20 |
| 95% CI | 27.58-37.79 | 18.93-33.54 |
| IRR | ref | **0.78** |
| | First serious AE | |
| PY for first serious AE | 935 | 270 |
| n. of serious AE | 56 | 9 |
| IR | 5.99 | 3.33 |
| 95% CI | 4.61-7.78 | 1.73-6.40 |
| IRR | ref | **0.56** |
| | First infection | |
| PY for first infection | 793 | 265 |
| n. of infection | 80 | 11 |
| IR | 10.09 | 4.16 |
| 95% CI | 8.10-12.56 | 2.30-7.51 |
| IRR | ref | **0.41** |
| | First serious infection | |
| PY for first serious infection | 964 | 284 |
| n. of serious infection | 30 | 2 |
| IR | 3.11 | 0.70 |
| 95% CI | 2.17-4.45 | 0.18-2.82 |
| IRR | ref | **0.23** |

PY: person-years; IR: incident rate per 100 person years; IRR: incident rate ratio; 95% CI: 95% confidence interval; T2T: treat-to-target; AE: adverse event.

founders on achieving remission or LDA, etanercept and the newer bDMARDs seemed to be more effective than infliximab or adalimumab whereas total steroid dose >500mg and SJC (6-10) were found to be negative predictive factors for remission or LDA (data not shown).

*Incident rates and ratios of adverse events*

Delayed bDMARDs administration on the basis of the "usual care" tradition was accompanied by more frequent and severe AEs, compared to administration according to T2T strategy (Table III). In the first group 155 patients were recorded with at least one AE (56 patients with serious), of which 80 patients had at least one infection (30 a serious one). In T2T group, there were 47, 9, 11 and 2 patients with at least one AE, serious AE, infection and serious infection respectively. The corresponding IRR for the T2T group was 0.78 for the 1rst observed AE, 0.56 for the first serious AE, 0.41 for the 1rst infection and 0.23 for the 1rst serious infection. Table IV illustrates the type of total AEs and infections (irrespective of AEs per person) in both groups. In a subgroup analysis we found that a greater incidence of cancer was noticed in patients of usual care group. There were 15 new cases of cancer (non-melanoma skin cancer=2, lung=2, lymphoma=5, breast=2, urinary tract=3, blood=1) compared with only one case of cancer (urinary tract) in T2T group. The IR of the first group was 1.99/100PY compared to 0.4/100PY of the second group ($p$=0.027). Nine of 16 cases had not reported any potential risk factor for cancer development. Mean duration of sDMARD treatment, before bDMARD initiation, was 113 months (range 17–299) whereas mean duration of bDMARD treatment was 41 months (range 5–123).

*Association of the treatment group with the risk of first AE or infection*

The KM plots (Fig. 3) depicted that the risk of first infection (irrespective of severity) was significantly higher for the usual care group compared to T2T group ($p$=0.002 for first infection and $p$=0.03 for first serious infection). The risk for the first AE and serious AE was also marginally statistically significantly higher ($p$=0.069 and 0.077 respectively) in the usual care group.

After controlling for potential confounders, it was found that the risk for a serious AE remained significantly high-

**Table IV.** Total adverse events during biologic treatment in rheumatoid arthritis patients (irrespective of AE per person).

| Adverse events during treatment | Usual care group (no of patients=250) (no of total AE=390) | T2T group (no of patients=113) (no of total AE=91) |
|---|---|---|
| Infections | 151 (38.7%) | 15 (16.5%) |
| Pulmonary | 78 | 4 |
| Urinary | 34 | 3 |
| Tuberculosis | 3 | |
| Herpes viruses | 9 | |
| Skin-mucous membrane | 7 | 3 |
| Bones-joints | 5 | 3 |
| Viral hepatitis | 2 | |
| Gastroenteritis | 4 | 1 |
| Endocarditis | 1 | |
| Meningitis | 1 | |
| Peritonitis | 1 | |
| Sepsis | 1 | |
| Other | 5 | 1 |
| Cancer | 15 (3.8%) | 1 (1.1%) |
| Liver function tests | 33 (8.5%) | 27 (29.7%) |
| Cardiovascular events | 29 (7.4%) | 5 (5.5%) |
| Skin-mucous membrane | 30 (7.7%) | 9 (9.9%) |
| Allergy | 60 (15.4%) | 11 (12.1%) |
| Dyslipidemia | 23 (5.9%) | 9 (9.9%) |
| Gastrenterologic events | 10 (2.6%) | 3 (3.3%) |
| Blood disorders | 10 (2.6%) | 4 (4.4%) |
| Renal disorders | 1 (0.3%) | 2 (2.2%) |
| Drug-induced SLE | 4 (1.1%) | |
| Peripheral neuropathy-polyneuritis | 2 (0.6%) | 2 (2.2%) |
| Other adverse events | 22 (5.6%) | 3 (3.3%) |

bDMARDs: biologic disease-modifying anti-rheumatic drugs; SLE: systemic lupus erythematosus; T2T: treat-to-target.

er for the usual care group (HR=0.42, 95% CI 0.18–0.97, $p$=0.041) (Table II). Nevertheless, patients in T2T group were at least twice likely to have a reduced risk for any infection (HR=0.49 for first infection and HR=0.24 for serious infection), although the findings were marginally non-significant ($p$=0.052 and 0.065, respectively).

Considering the other covariates in the models, we found that extra-articular manifestations increased the risk for any AE (irrespective of severity), progression of age was important for the first AE (mild or serious) and first serious infection, whereas patients with ESR >40mm/h were more vulnerable to infections (data not shown).

## Discussion

Many studies have shown that T2T strategy offers a better outcome and improved quality of life in patients with RA, compared with usual care (12-15). Nevertheless, most of these studies involved comparative groups with different treatment options, mainly sDMARDs versus combination of sDMARDs and bDMARDs (16-19).

In line with the previous findings we have shown that T2T strategy according to EULAR recommendations for bDMARDs, as compared to "usual care" tradition, was more efficacious in treating RA patients. Patients treated aggressively were 71% more likely to achieve a good response (remission or LDA). No significant difference on the efficacy was noticed between of the three classical anti-TNF-α inhibitors. Our findings are in the same line with findings of other studies in literature. Delayed initiation of infliximab and adalimumab resulted in a rather worse outcome compared with the outcome after proper use, regarding quality of life and radiographic damage (20-23).

The novel evidence of this report however is the evaluation of the hypothesis that T2T strategy offers a better safety profile in RA patients when bDMARDs are required. We, as well as others, have previously shown that AEs, mild or serious, are rather common in patients receiving bDMARDs compared to sDMARDs (24, 25). To our knowledge, this is the first study showing that the safety of bDMARDs administered according to EULAR guidelines is much better as compared with their use according to usual care tradition in patients with RA. Frequency and severity of AEs, especially infections, were substantially reduced in T2T group, supporting our hypothesis. It seems that prompt response to therapy and minimisation of active inflammation reduces the risk for AEs. On the contrary, delayed suppression of inflammation, due to less aggressive therapy is directly related to increased frequency of AEs. It has been shown that HDA was directly related to increased rates of infections and a prompt response to treatment may reduce that risk (26). Increase of DAS-28 by 0.6, predisposes to an increase of the frequency of infections by 4% for mild and by 25% for serious ones, demanding hospital admission. Not only infections, but also an increased risk for heart failure was found in patients with HDA and the degree of heart failure was reduced after successful treatment with anti-TNF-α agents (27).

A striking finding was the greater incidence of cancer in patients with delayed administration of bDMARDs. Most published studies comparing bDMARDs with sDMARDs found conflicting results regarding the incidence of cancer in patients with bDMARDs (28-31). Whether a T2T strategy, related with a quick and successful reduction of disease activity, reduces the risk of cancer compared to more conservative treatment approaches has not been evaluated so far. There is some evidence that lymphoma or other cancer risk is related to the severity of disease, while accumulated evidence shows that chronic inflammation predisposes to cancer development (32, 33). Our data support this notion, although further studies are needed to confirm these results. The IR of cancer in the general Greek population is estimated from 0.235 to 0.45/100PY (34, 35). In our study, IR in T2T group was quiet similar, a finding that is in accordance with the well established knowledge of similar or modestly elevated cancer

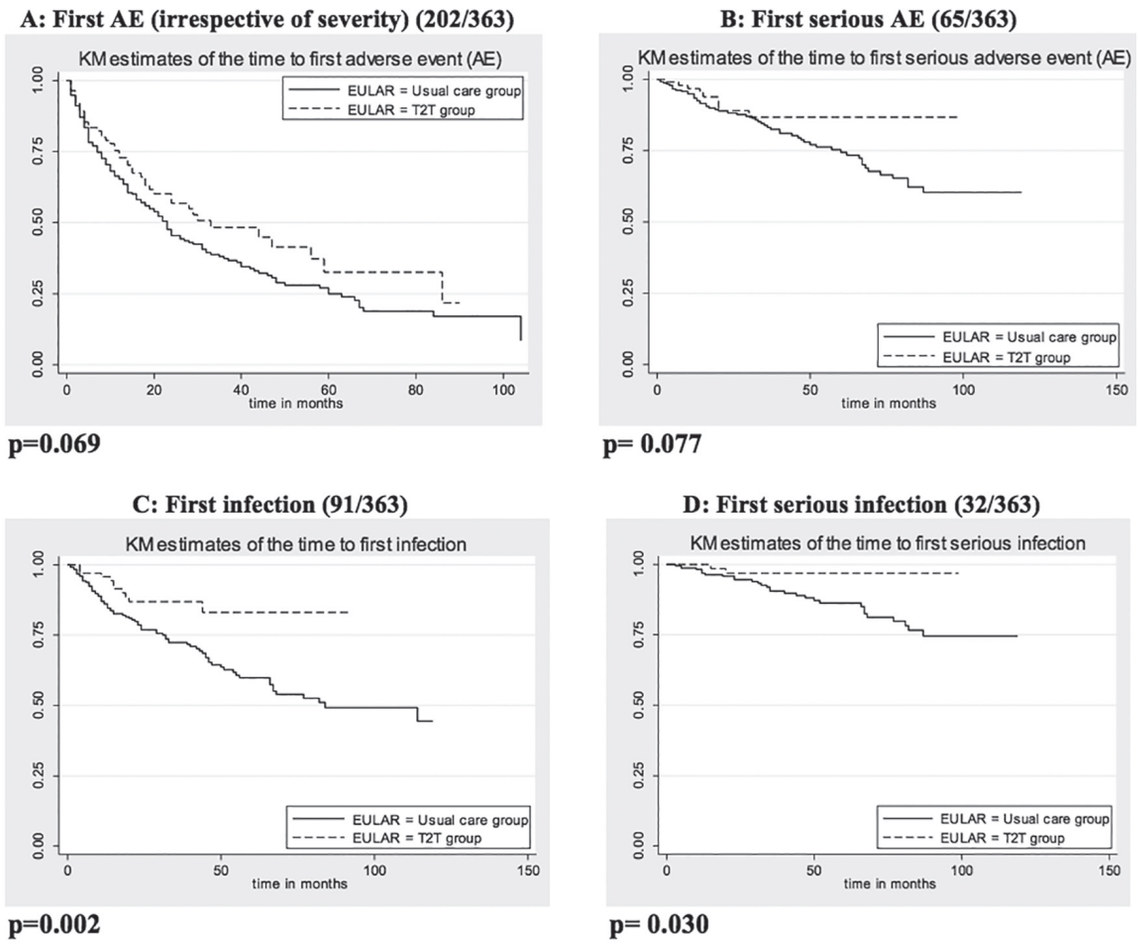



**Fig. 3.** Kaplan-Meier plots depicting disease free survival to the first adverse or serious adverse event (A, B, respectively) and the first infection or serious infection (C, D, respectively) for 363 patients treated with the first bDMARD according to T2T or to usual care strategy.

risk in patients with RA, compared to general population (36). In contrary, the risk of cancer in usual care group was significantly increased, supporting the aforementioned hypothesis.

An interesting finding of our study was that the proportion of men was higher in the T2T group as compared to the usual care group (Table I). The gender difference may be attributed to the fact that the need for biologic treatment among men was rather common due to the severity of their disease, compelling initiation of T2T therapy. On the contrary the previous conservative policies regarding initiation biologics were applied equally to men and women thus the end result was a different proportion of men in the T2T group.

The retrospective nature, the relatively small number of patients and missing data of Health Assessment Questionnaires are limitations of the present study. Nevertheless, the long duration of observation strengthens enough our findings. The detailed and continuous recording for years, of complete information about patients' condition and treatment, allows us to give a clear, real-world, picture of RA patients, with all their co-morbidities and unpredictable factors that affect doctor's judgment.

In conclusion, prompt initiation of bDMARDs in patients with RA, according to EULAR recommendations for T2T strategy, is accompanied by higher remission or LDA rates and reduced frequency of AEs, infections and cancers. These findings are striking enough to alert clinicians that intensive treatment has multiple benefits regarding efficacy and safety.

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