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Research Article

Title

Comparative effectiveness of first-line biologic monotherapy use in rheumatoid arthritis. RECord-linkage On Rheumatic Disease study on health care administrative databases.

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Abstract

Objective

These analyses aim to comparatively evaluate the persistence on treatment of different biological disease-modifying antirheumatic drugs (bDMARDs) when administered in monotherapy compared to combination with conventional synthetic (cs)DMARDs in rheumatoid arthritis (RA) patients receiving first-line biologics.

Design

This is a retrospective observational study on Administrative Healthcare Databases.

Methods

Data were extracted from healthcare databases of the Lombardy Region, Italy (2004-2013), as a part of the RECord-linkage On Rheumatic Diseases (RECORD) study, on behalf of the Italian Society for Rheumatology (SIR). Analyses included RA patients starting first-line approved course of bDMARDs and evaluated drug survival by using Cox proportional hazard models. Results are presented as hazard ratios (HR) and 95%CI, crude and adjusted for pre-specified confounders (age, sex, disease duration, Charlson Comorbidity Index (CCI), previous infections, use of concomitant glucocorticoids or NSAIDs).

Results

4478 RA patients were included (17.84% monotherapy). bDMARD monotherapy was associated with longer disease duration, higher CCI, lower glucocorticoids and NSAIDs use. Compared to monotherapy, combination associated with a lower risk of failure (adjusted HR 0.79, 95%CI 0.72-0.88). Among monotherapies, considering etanercept as reference, adalimumab (1.28, 1.03-1.59) and infliximab (2.41, 1.85-3.15) had higher risk of failure. Concomitant methotrexate (0.78, 0.70-0.87), leflunomide (0.80, 0.65-0.98), or csDMARD combinations (0.77, 0.68-0.87) reduced the risk of bDMARD withdrawal.

Conclusion

Adalimumab and infliximab monotherapies show lower retention rate compared with etanercept. Concomitant methotrexate, leflunomide and csDMARD combination associate with longer survival on bDMARD. Our data confirm the effectiveness of the current practices in the choice of etanercept as first line anti-TNF monotherapy and strengthen the currently recommended use of bDMARDs in combination with csDMARDs.

Strengths and limitations of this study

- This study provides results from administrative databases, following a previous study with the complete validation of classification algorithms for the identification of patients with rheumatoid arthritis (RA) at the population level through healthcare administrative databases.
- This study, as expected by study design, has no loss to follow up and allows the analysis of a large sample of patients.
- Limitations of the RECORD study include the absence of specific disease clinical outcomes, in particular no information are available about disease activity and radiographic progression.

Introduction

Biological disease modifying antirheumatic drugs (bDMARDs) are recommended in association with non-biological (conventional synthetic) disease-modifying drugs (csDMARDs) in the treatment of rheumatoid arthritis (RA). As stated by recent updated 2016 EULAR recommendations for the management of RA[1], bDMARDs should be combined with a csDMARD because of a superior efficacy of combination therapy. Recommendations suggest using tocilizumab (TCZ) or a novel targeted synthetic molecule (tsDMARD) as tofacitinib or baricitinib when combination is not possible. Not only methotrexate (MTX) is useful in combination therapy, but other csDMARDs can be also considered.

The better performance of bDMARD combination therapy with csDMARDs over bDMARD monotherapy has been clearly established both in terms of efficacy and retention rate. A recent meta-analysis of the Hazard Ratios (HRs) of bDMARDs discontinuation shows a 23% lower risk of drug withdrawal for any cause in patients treated also with csDMARDs[2]. A possible pharmacodynamic explanation is linked to an additive effect in the inhibitory profile of the combined drugs. In particular, differences between biologics exist and MTX plus adalimumab (ADA) inhibits more biological pathways compared to MTX plus TCZ, suggesting a synergistic effect of MTX in immunosuppression which differs across drugs[3]. A pharmacokinetic effect of incremental doses of MTX in enhancing serum concentrations of ADA was also observed[4]. Moreover, the immunogenicity of biologics, in terms of occurrence of anti-drug antibodies, is lower in combination therapy and MTX reduces the incidence of the appearance of such antibodies[5,6]. The effect of csDMARDs other than MTX in reducing immunogenicity of TNF-inhibitors (TNFi) is still unknown. TCZ and etanercept (ETA) share low immunogenicity[7,8]; MTX association did not influence the production of anti-TCZ[9] and anti-abatacept (ABA) autoantibodies and, when autoantibodies occur, they are not associated with adverse events or

discontinuation of therapy[10]. Reduction in disability and radiographic progression are also superior in combination regimens[11].

Limited data are available about the best biological treatment choice in real-life when a biologic monotherapy is necessary for biologic-naïve patients. In clinical practice, contraindications to MTX or early intolerance to csDMARDs are frequently observed, and clinicians need to start a biologic monotherapy in these cases; the result is that RA patients are treated with monotherapy nearby in one third or even more cases[12–16].

Differently from randomized controlled trials (RCTs), data from observational studies or registries explore the utilization of monotherapy in real-life clinical practice[2] and persistence in therapy is considered a good indirect and composite measure of effectiveness, safety and tolerability, reflecting the long-term impact on the course of the disease. Data of real-life overall persistence show that monoclonal TNFi are burdened by a higher risk of drug failure compared to ETA[2]. Limited data are available for non-TNFi.

Objective of this analysis was to assess, in RA patients receiving first-line approved biological therapy, the comparative effectiveness (expressed in terms of drug survival) of different bDMARDs when administered in monotherapy compared with combination therapy, accordingly to real-life clinical practice and in compliance with local regulatory approvals. Secondary objectives were to characterize features of patients starting monotherapy and to evaluate the specific effect of MTX combination therapy compared with other csDMARDs association regimens in determining persistence of bDMARD co-therapy.

To answer these questions, we took advantage by the RECord-linkage On Rheumatic Diseases (RECORD) dataset, including data from administrative health database (AHD) of the Lombardy

region (Italy), analysing bDMARDs and concurrent drug exposures of all the first courses of bDMARDs of RA patients between 2004 and 2013.

Materials and Methods

Study Design and Setting

This is a retrospective observational study on AHD of Lombardy Region, Italy (>10,000,000 inhabitants). Access to data was granted by the General Directorate of Health for the purpose of the RECORD study, a project promoted by the Italian Society for Rheumatology (SIR) aiming to set up a national surveillance system to monitor the health burden of rheumatic diseases in Italy using AHD. The protocol was approved by the ethical committee of the Pavia University Hospital. Data included were retrieved between 1st of January 2004 and 31st of December 2013.

Participants and variables

The design of the RECORD study includes a database population of patients with RA and 4 age and sex-matched controls from the general population. Patients with RA were identified through co-payment exemption code 006.714.0, based on its previously demonstrated high specificity (96.39%) and high sensitivity (77.08%) for RA[17], in line with other studies following a similar methodology[18,19].

Study population was defined among patients with RA and at least one delivery of first-line approved bDMARDs (abatacept (ABA), adalimumab (ADA), certolizumab (CTZ), etanercept (ETA), golimumab (GOL), infliximab (INF) and tocilizumab (TCZ)). Rituximab (RTX) was excluded due to the local limitation in first-line deliverability of this drug in RA patients. The exposure to non-steroidal anti-inflammatory drugs (NSAIDs), daily mean glucocorticoid (GC) dosage (expressed in terms of prednisone equivalent, mg per day) and to specific csDMARDs (MTX, Leflunomide (LFN), Cyclosporine A (CYA), Hydroxychloroquine (HCQ) or Sulphasalazine (SSZ)) was defined by the drug delivery recorded in the administrative database.

Data included demographics (birth date, gender, death date or embarkment, drug delivery (Anatomic-Therapeutic Chemical – ATC) - code, date of drug delivery, quantity), exemptions (exemption code, date of exemption), outpatient services (code and date) and hospital discharge forms (HDF) including information on beginning and end of hospitalization, International Classification of Disease, 9th revision, Clinical Modification (ICD-9-CM) diagnoses and Disease Related Group – DRG. Previous bacterial infections were considered if hospitalization for bacterial infection or an antibiotic treatment course of over 14 days occurred in the previous year[20].

Statistical methods

The primary outcome was persistence with first-line bDMARD, which was defined as the length of time between drug delivery plus drug coverage. A patient was considered exposed to a specific treatment from the first prescription of drug until the last one plus 6 months, in order to consider the coverage period of drug also after its withdrawal, or until the first prescription of the subsequent drug. Censoring was defined at treatment stop date plus drug coverage or until the start of a new bDMARD, death or at the end of established follow-up, whichever came first. Drug persistence in bDMARD therapy was compared using Cox proportional Hazard models. Results were presented as HR and 95%CI, crude and adjusted for pre-specified confounders (sex, age, disease duration, Charlson Comorbidity Index (CCI)[21], concomitant use of NSAIDs, GCs average dosage and previous bacterial infections). A secondary analysis, focused on the role of each associated csDMARD in bDMARD persistence, was analyzed by the same mechanism (firstly considering combination biologics as a whole and then investigating the interaction between different csDMARDs and each bDMARD). A sensitivity analysis was performed to investigate if different periods of bDMARDs prescription could have influenced persistence data (a distinction was made before and after 31st December 2009, according to changes occurred in local bDMARDs deliverability).

All the analyses were performed using the Stata11 software (STATA Corporation, College Station, Texas, USA) and R statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Results

Study population and Descriptive Data

A total of 4478 RA patients who had their first-line bDMARD delivery were included (13728 person/time). 3472 were women (77.53 %); mean age (standard deviation, SD) at bDMARD exposure was 55.48 (12.69) years with a modal disease duration of over five years. No missing data nor lost to follow-up were recorded, nor expected by design. A mean (SD) CCI of 1.16 (0.48) was observed (Table 1).

bDMARD monotherapy was administered to 799 patients (17.84%) while 3679 (82.16%) experienced csDMARDs association. Most prescribed bDMARDs were ETA (1787 patients, 39.91%), ADA (1143, 25.52%) and INF (861, 19.23%). ETA was the most prescribed drug out of monotherapy (385 patients, 48.19%) and in combination group (1402 patients, 38.11%) (Table 2).

Among concomitant csDMARD therapy, MTX was the most commonly prescribed (2297 patients had only concurrent MTX, 62.44%); 223 only concurrent LFN (6.06%), 151 concurrent HCQ (4.10%), 43 SSZ (1.17%), 41 CYA (1.11%). 924 patients (25.12%) experienced a combination of different csDMARDs; in this group a total of 827 patients received MTX, 254 LFN, 131 SSZ, 619 HCQ, 116 CYA.

451 bDMARD monotherapies were started before 31st December 2009 (252 ETA, 136 ADA, 62 INF, 1 ABA, no TCZ, CTZ and GOL) and 348 after 1st January 2010 (133 ETA, 65 ADA, 47 TCZ, 33 ABA, 30 CTZ, 21 GOL and 19 INF).

Factors influencing monotherapy

Monotherapy was associated with longer disease duration, a higher CCI (in particular hepatic and renal disease and heart failure), lower use of GCs and NSAIDs (Table 1).

Table 1. Clinical and demographic features of the study population including 4478 RA patients and their distribution in bDMARDs mono- and combination therapy.

Demographic characteristics	*Study population*	*Monotherapy (N. 799)*	*Combination (N 3679)*	*p*
Mean age (SD, years)	55.48 (12.69)	54.90 (12.97)	55.61 (12.62)	0.136
Female, n (%)	3472 (77.53)	614 (76.85)	2858 (77.68)	0.607
Clinical characteristics				
Disease duration N (%)				
• < 1 years	1028 (22.96)	153 (19.15)	875 (23.78)	<0.001
• > 1 to ≤ 2 years	1106 (24.7)	188 (23.53)	918 (24.95)	
• ≥ 3 to ≤ 5 years	1064 (23.76)	171 (21.40)	893 (24.27)	
• > 5 years	1280 (28.58)	287 (35.92)	993 (26.99)	
Number of comorbidities = 0 N (%)	3941 (88.01)	683 (85.48)	3258 (88.56)	0.004
Number of comorbidities = 1 N (%)	416 (9.29)	80 (10.01)	336 (9.13)	
Number of comorbidities = 2 N (%)	105 (2.34)	30 (3.75)	75 (2.04)	
Number of comorbidities > = 3 N (%)	16 (0.36)	6 (0.75)	10 (0.27)	
Charlson Comorbidity Index *, Mean (SD)	1.16 (0.48)	1.22 (0.60)	1.15 (0.45)	0.009
CHD, N (%)	66 (1.47)	16 (2.00)	50 (1.36)	0.193
Heart Failure, N (%)	12 (0.27)	5 (0.63)	7 (0.19)	0.047
Vascular Pathology, N (%)	10 (0.22)	4 (0.50)	6 (0.16)	0.086
Dementia, N (%)	1 (0.02)	1 (0.13)	0 (0.00)	0.178
COPD, N (%)	49 (1.09)	11 (1.38)	38 (1.03)	0.451
Mild Hepatic disease **, N (%)	73 (1.63)	24 (3.00)	49 (1.33)	0.002
Diabetes, N (%)	276 (6.16)	41 (5.13)	235 (6.39)	0.195
Renal Disease, N (%)	32 (0.71)	18 (2.25)	14 (0.38)	<0.001
Neoplasm **, N (%)	67 (1.50)	16 (2.00)	51 (1.39)	0.198
Leukemia / Lymphoma, N (%)	1 (0.02)	1 (0.13)	0 (0.00)	0.178
Previous Infections, N (%)	822 (18.36)	140 (17.52)	682 (18.54)	0.501
Concomitant NSAIDs, N (%)	3386 (75.61)	485 (60.70)	2901 (78.85)	<0.001
Concomitant GCs, N (%)	3045 (68.00)	428 (53.57)	2617 (71.13)	<0.001
GCs dose (mg/day), mean (SD)	2.23 (3.08)	1.85 (3.32)	2.31 (3.01)	<0.001

CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease; AIDS: Acquired Immunodeficiency Syndrome.
** Diabetes with end-organ damage, AIDS, cerebrovascular disease, peptic ulcer and hemiplegia are not shown due to absence of cases in monotherapy group.*
*** Severe hepatic disease and metastatic neoplasms are not shown due to absence of cases in both groups.*

Table 2. Distribution of different bDMARDs in mono- and combination therapy with csDMARDs

bDMARDS	*Study population*	*Monotherapy (N. 799)*	*Combination (N 3679)*
ABA N (%)	189 (4.22)	34 (4.26)	155 (4.21)
ADA N (%)	1143 (25.52)	201 (25.16)	942 (25.60)
CTZ N (%)	156 (3.48)	30 (3.75)	126 (3.42)
ETA N (%)	1787 (39.91)	385 (48.19)	1402 (38.11)
GOL N (%)	151 (3.37)	21 (2.63)	130 (3.53)
INF N (%)	861 (19.23)	81 (10.14)	780 (21.20)
TCZ N (%)	191 (4.27)	47 (5.88)	144 (3.91)

Risk of bDMARD failure

Compared to monotherapy, combination with at least one csDMARD was associated with a lower risk of drug failure (crude HR 0.77, 95%CI 0.69-0.85; adjusted HR 0.79, 95%CI 0.72-0.88). Among patients in bDMARD-monotherapy, considering ETA as reference, the adjusted HR for bDMARD failure was 1.28 for ADA (95%CI 1.03-1.59) and 2.41 for INF (95%CI 1.85-3.15) (Figure 1); ABA monotherapy was associated with a reduced - but not statistically significant - risk of failure, while TCZ was almost equal to ETA. Otherwise, among combination therapies, only INF was significantly inferior compared with ETA monotherapy. The risk of failure evaluated for the other bDMARDs was not statistically different from ETA monotherapy.

Influence of different csDMARDs in persistence in bDMARD treatment

Considering specific combination therapy and taking bDMARD monotherapy as reference, concurrent csDMARDs significantly reduced the risk of bDMARD withdrawal (adjusted HR 0.78 for MTX alone, 95%CI 0.70-0.87; HR 0.80 for LFN alone, 95%CI 0.65-0.98; HR 0.77 for combination of different csDMARDs, 95%CI 0.68-0.87) (Figure 2), while no statistical significant improvement in drug survival was observed for SSZ, HCQ or CYA when used as the single associated csDMARD.

The analysis of different csDMARDs in determining persistence of different bDMARD treatment showed that MTX alone or in combination with other csDMARDs positively influenced persistence in INF treatment, while other associations between csDMARDs and bDMARDs did not significantly modify the concomitant biologic drug survival.

Sensitivity analysis

After stratification in different periods of time (before and after 31st December 2009) an increase in the previous reported risk of drug failure for INF was observed (HR 2.72, 95%CI 1.51-4.90). The risk of ADA failure remains elevated compared to ETA monotherapy, but differences according to the time period were no longer significant (HR 1.17, 95%CI 0.70-1.96); the risk of failure for other

bDMARDs remains not significantly different from ETA (Supplementary file 1). A sub-analysis of the patients receiving ADA monotherapy after 1st January 2010 showed that in this group a proportional higher number of males was present (p=0.004), with longer disease duration (p<0.001) and higher CCI (p=0.018).

Discussion

Using bDMARDs as monotherapy in clinical settings is a common practice for RA patients and recognised by health authorities although current guidelines recommend combining them with csDMARDs. The aims of this study were to describe persistence and factors associated with starting biologic monotherapy in a real-world setting. In our study, monotherapy was common and observed in approximately 1 out of 5 biologic-naive patients with RA initiating a biologic agent (17.8%). In previous biologics registries and claims database studies, 12–39% of patients were taking biologics as monotherapy[22–24].

From a practical perspective, it seems even more important to investigate those factors which may drive prescribing monotherapy. Indeed, bDMARDs monotherapy could be representative of a subgroup of patients with a more difficult disease management[25]. It has been reported that older patients, with longer disease duration and multiple comorbidities, lower body mass index (BMI) and higher disease activity show higher probability to undergo monotherapy[16,22,25,26]. Concomitant use of glucocorticoids predicts higher bDMARD discontinuation, reflecting a much severe course of the disease[2,23]. Accordingly, in our retrospective study based on AHD, we have observed a significant association between monotherapy and longer disease duration and a higher number of comorbidities. As expected, hepatic and renal diseases were the most limiting factors for csDMARDs association. NSAIDs and GCs were negatively associated with monotherapy, likely reflecting contraindication to these drugs due to concomitant comorbidities.

As demonstrated by the majority of published real-life studies and RCTs, our study confirms that bDMARD risk of failure is significantly lower in combination with csDMARDs (21% lower risk of drug withdrawal compared to monotherapy). Concerning monotherapy, in a Swiss study of retention rate which analyses data from Swiss Clinical Quality Management Registry (SCQM-RA) between 2004 and 2013[25], 27% of all biologics therapeutic courses was initiated as

monotherapy (the higher percentage of monotherapy was for CTZ with 46%; 35% ETA; 35% TCZ; 29% ABA; 26% ADA; 23% RTX; 17% GOL and 14% INF) and a further 13% experienced a transient phase of monotherapy overtime; discontinuation of bDMARD occurred in 63% (1545/2453) and the adjusted HR for discontinuation of biologic monotherapy versus combination was 1.15 (95%CI 1.03-1.30, p=0.018), although differences between the two groups were relatively modest. Treatment failure was influenced not only by the type of bDMARD but even by gender, number of previous bDMARDs, year of initiation of the receiving drug, seropositivity, disease duration and activity. TNFi strongly impact these data, being historically the first bDMARD entered in clinical practice and accounting for about 80% of therapeutic courses; therefore, conclusive results are still lacking. Overall, the type of bDMARD is certainly one of the most important factors influencing persistence, and INF monotherapy is burdened by the higher rate of withdrawal[2,23,27]. Globally, monoclonal antibodies against TNF-alfa share higher discontinuation compared to ETA[2,28]; whether the global higher immunogenicity of monoclonal antibodies is strictly responsible for this difference is still matter of debate. In an observational study, Kristensen et al.[29] stand out a higher adherence in first-line ETA-treated patients compared to INF; concomitant MTX was associated with better persistence in both groups but significantly higher for ETA. In a 12-years retention rate study of first-line TNFi, Favalli et al.[30] demonstrated a higher risk of drug failure for ADA (HR 2.89, 95%CI 2.2-3.78) and INF (HR 2.56, 95%CI 1.92-3.4) compared to ETA, similarly to what is reported by a French multicentric study by Frazier-Mironer[31] and the GISEA registry[32]; MTX-users in combination with biologic shared higher retention rate compared with TNFi monotherapy (HR 1.48, 95%CI 1.18-1.86). Jorgensen et al.[23] analysed 775 pts in the Danish registry and showed that persistence in monotherapy was significantly higher for all biologics compared to INF (HR of withdrawal 2.53 for INF compared to other bDMARDs, 95%CI 1.70-3.77, p <0.001) and these features were indipendent of the number of previous biologics. In German RABBIT registry, a longer persistence was found in combination therapy with TNFi but remission

rates were not significantly different from monotherapy group[14]. The south Swedish SSATG registry[33] evaluated differences in biologics monotherapy persistence in different biologics courses over 6 years and highlighted a significant difference among bDMARDs with highest retention rates observed for RTX and ETA. In RADIUS registry[34], which analyzed different efficacy between ETA, INF and csDMARDs therapy, patients receiving either ETA plus MTX (adjusted OR 1.29, 95%CI 1.09-1.52, p<0,01) or ETA monotherapy (OR 1.23, 95% CI 1.02-1.47, p<0,05) were more likely to achieve a modified ACR20-response at 12 months than patients receiving MTX alone, INF plus MTX or INF alone; persistence in therapy however was higher for INF plus MTX (71% of INF group persisted in therapy after 12 months; versus 69% of ETA monotherapy, 67% INF alone and 61% ETA plus MTX); noteworthy cost of the therapy was claimed as a significant cause of discontinuation of biologic therapy in this registry (up to 6% of ETA monotherapy changed treatment due to high costs). The ACT-iON observational study[35] explored different persistence rates among first-line TNFi and TCZ and showed a better persistence for TCZ compared to TNFi as a whole; a comparison between first-line monotherapies was not possible due to the low number of cases. Our data are in keeping with current literature and show a lower persistence for first-line monoclonal TNFi (ADA and INF) monotherapy compared with ETA monotherapy, suggesting that these bDMARDs should be avoided when a TNFi monotherapy is thought to be necessary.

Data from RTCs confirm this tendency among TNFi, either in terms of retention rate as well for radiological outcomes, but long term head-to-head comparative trials among different bDMARDs specifically designed to test this outcome are lacking. With regard to non-TNFi, data about a real superiority of combination therapy compared to monotherapy are controversial[7,26]. A pan-European analysis of registries including nearby 3400 pts showed that retention of ABA was not influenced by csDMARDs co-therapy[7]. TCZ has gained the reputation to be the best bDMARD to utilize in monotherapy and the only one with a satisfactory durability[12,13,36] and cost-

effectiveness[37]. However, also for this drug, association strategy has demonstrated to be useful in clinical trials giving some advantages when compared with monotherapy. In ACT-RAY trial, after 2 years, a difference in radiographic progression was observed favoring combination regimen with MTX[38] and, in a recent post-hoc sub-analysis of ACT-SURE study, concomitant csDMARDs helped to achieve low disease activity earlier than in TCZ monotherapy[39], similarly to what demonstrated by Kaneko et al. in SURPRISE study[40]. Conversely, other studies did not show particular advantages in terms of clinical efficacy of TCZ combination therapy over monotherapy[41,42]. In ADACTA study[43] TCZ monotherapy reduced significantly disease activity score (DAS) and Clinical Disease Activity Index (CDAI) compared to ADA monotherapy after 24 weeks, in a head-to-head comparison between monotherapies. Our study confirms a similar persistence rate between non-TNFi monotherapy compared to combination, but the small size of our sample and the calendar-period of the analysis does not allow a conclusive remark.

Our data show that either MTX or LFN or combination of different csDMARDs significantly increase bDMARDs persistence rate, while CYA is associated with a higher (but not significant) rate of drug failure. Previous reports on the benefits of combining different csDMARDs with bDMARDs have shown contrasting results; Soliman et al.[16] explored the role of different csDMARDs intervention in biological persistence in a real-life study which evaluated persistence in over 10,000 pts from a British registry and stated that MTX combination was linked to a better persistence of the first TNFi when compared to no csDMARDs, LFN or SSZ but the best overall persistence was seen among pts receiving TNFi in combination to MTX and either SSZ or HCQ or both, in line with our results. Similarly, Manders et al. found a similar persistence rate in TNFi plus MTX group compared to TNFi plus MTX plus others[44]. De Stefano et al.[45] reported a similar efficacy and safety profile for TNFi combined with either MTX or LFN in Early RA, but univocal data for LFN combination to bDMARDs are lacking and limited by the high number of associations with INF[46].

Conversely, Kristensen et al.[29] demonstrated that concomitant MTX, but not other csDMARDs, was associated with a better persistence with first-line ETA or INF therapy, but significantly higher for ETA. A positive influence in terms of efficacy has been observed for LFN combined with RTX in GERINIS study[47] and in CERERRA collaboration[48].

When stratifying by calendar year - subclasses, after the introduction of other bDMARDs in current recommended therapeutic approach, the risk of failure for INF monotherapy slightly increased, while ADA monotherapy became not statistically different from ETA. Higher number of comorbidities and longer disease duration in this subgroup could reflect the selection of a particular subset of patients for whom an acceptance of a sub-optimal control of disease activity has been made, despite a real efficacy of the drug. Afterwards, the reduction of the sample size after this stratification could have influenced the results as well as the prescription attitude of bDMARDs might have changed during the period of analysis. In fact, as shown by literature[2,25], the year of treatment could have influenced bDMARD retention rate, since rheumatologists are more prone to change biologics if more alternatives are available[27], although data about this issue are controversial[49].

Our study has some limitations. The different burden of prescribed bDMARDs (being ETA, ADA and INF the most prescribed ones) could have influenced our results; to this regard, GOL, CTZ and non-TNFi associated with a lower prescription rate and RTX was excluded due to the local limitation in first-line deliverability. We adjusted for pre-specified confounders but confounding of unmeasured factors could not be excluded (50). Furthermore, the design of the study could not differentiate between patients starting monotherapy “ab initio” and those reaching such monotherapy by a “step-down” process; despite this behavior accounts for only a small proportion[25], the overall prevalence could have been under-recognized due to specific design of trials and “real-life” databases[16]; anyway, characterizing such a population was out of the scope of our study which

focuses only on the first group ("ab initio" monotherapies). Other limitations are intrinsic in the AHD-based design of the study, in particular lack of control of data collected for non-clinical purposes and misclassification biases; furthermore clinical outcomes are lacking (absence of disease activity and radiological outcome data; specific causes of bDMARD failure or monotherapy prescription, such as patients' or physicians' preferences[22]; possible alternative therapeutic schemes, including spacing of the bDMARD scheduled administration; different dosages of csDMARDs co-therapy)[50].

However the RECORD study has some relevant strengths: its large sample size, allowing the examination of the effect of concomitant bDMARDs and csDMARDs, and the completeness of data without loss at follow-up. This is, to our knowledge, the first AHD-based study investigating different persistence rates in first-line biological monotherapies combining all bDMARDs approved as "first-line" treatment.

In conclusion, our study supports the currently recommended use of bDMARDs in combination with csDMARDs, underlining a higher risk of drug withdrawal for TNFi monotherapy compared with combination and suggesting that, among bDMARDs, ETA should be preferred over INF - and to lesser extent ADA - when a first-line monotherapy is necessary. Our results strengthen the positive influence of MTX, LFN or combination of csDMARDs in improving bDMARDs persistence.

Figure Legends

Figure 1

Crude and adjusted HR and 95%CI for bDMARD failure when administered in first-line monotherapy and in combination with csDMARDs.

Figure 2

Crude and adjusted HR and 95%CI for different csDMARDs in determining the risk of fist-line bDMARD failure.

Competing interests:

E. Silvagni; G. Carrara; A. Zanetti; C.A. Scirè: none to declare. A. Bortoluzzi: Sanofi, Alfa-Wasserman. M. Govoni: Pfizer, Abbvie, MSD, Roche, BMS, Sanofi, Lilly, Novartis, Celgene: fees for sponsorized lectures and/or partecipation in advisory boards.

Data sharing information:

No additional information are available.

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Authorship Criteria:

Substantial contributions to study conception and design: ES, AB, GC, AZ, MG, CAS

Substantial contributions to acquisition of data: GC, ES, AZ, CAS

Substantial contributions to analysis and interpretation of data: ES, AB, GC, CAS

Drafting the article or revising it critically for important intellectual content: ES, AB, GC, AZ, MG, CAS

Final approval of the version of the article to be published: ES, AB, GC, AZ, MG, CAS

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: ES, AB, GC, AZ, MG, CAS

No other potential author who fulfils the ICMJE Recommendations criteria has been excluded as an author.

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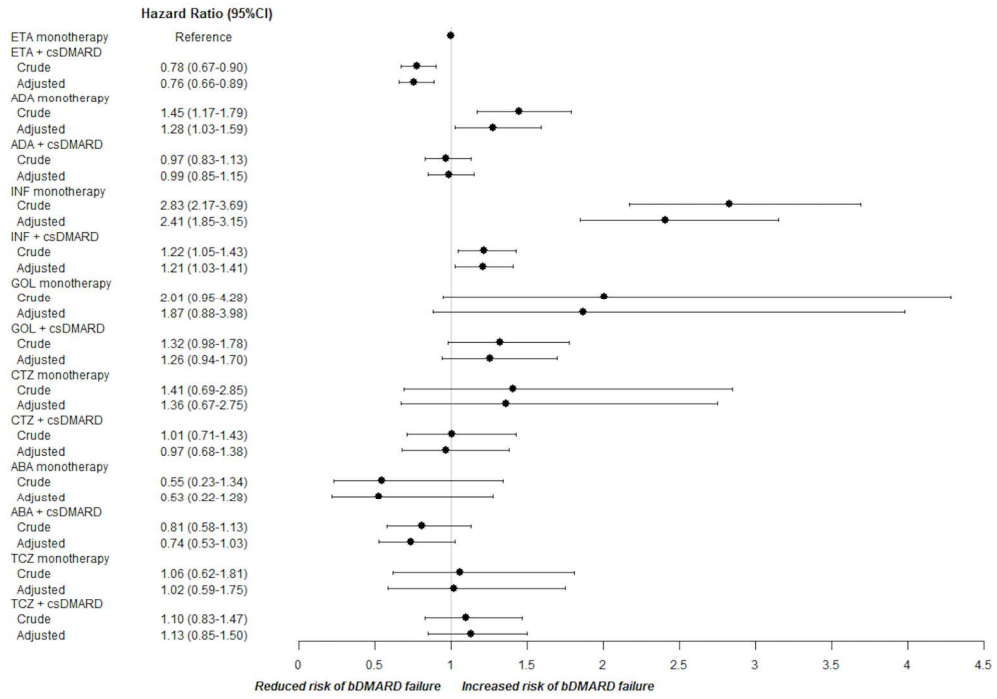

Figure 1
Crude and adjusted HR and 95%CI for bDMARD failure when administered in first-line monotherapy and in combination with csDMARDs.

163x114mm (300 x 300 DPI)

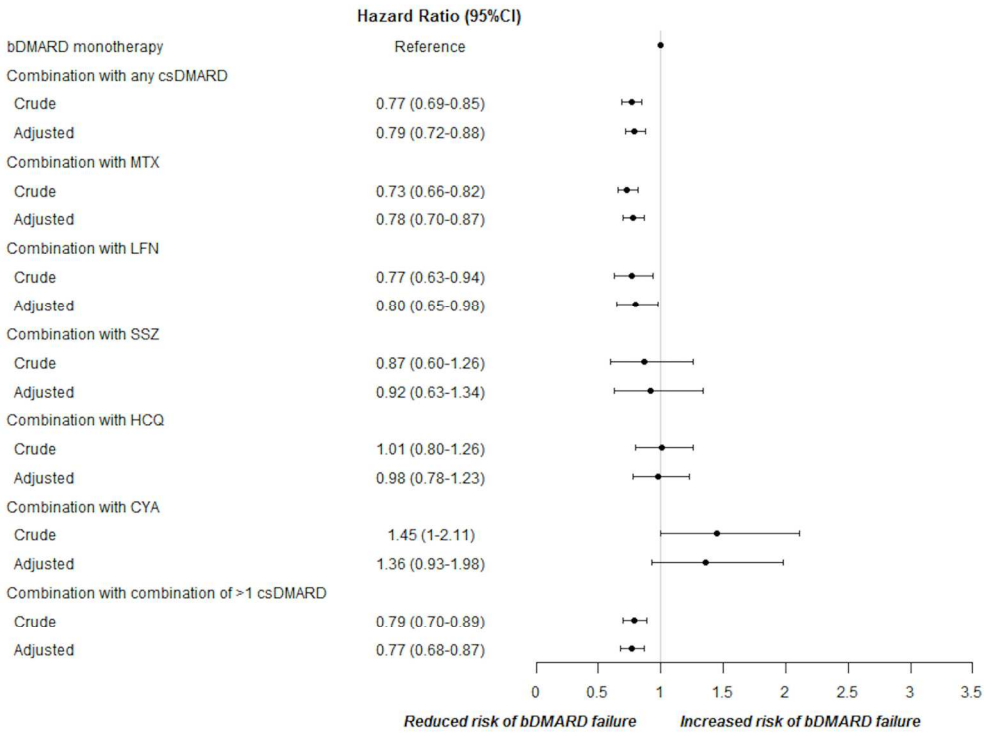

Figure 2
Crude and adjusted HR and 95%CI for different csDMARDs in determining the risk of fist-line bDMARD failure.

152x114mm (300 x 300 DPI)

Supplementary file 1. Risk of drug failure of different bDMARDs monotherapy before and after 31st december 2009.

bDMARD monotherapy	*Adjusted HR (95%CI) before 31st december 2009*	*p*	*Adjusted HR (95%CI) after 1st January 2010*	*p*
ETA monotherapy (385 patients)	1 (ref)		1 (ref)	
ADA monotherapy (201 patients)	1.40 (1.09 – 1.78)	0.008	1.17 (0.70-1.96)	0.554
INF monotherapy (81 patients)	2.20 (1.59 – 3.05)	<0.001	2.72 (1.51 – 4.90)	0.001
GOL monotherapy (21 patients)	*Not applicable**		1.38 (0.60 – 3.18)	0.447
CTZ monotherapy (30 patients)	*Not applicable**		1.08 (0.51 – 2.29)	0.843
ABA monotherapy (34 patients)	*Not applicable**		0.46 (0.18 – 1.15)	0.097
TCZ monotherapy (47 patients)	*Not applicable**		0.82 (0.45 – 1.48)	0.504

** Not applicable: based on the changes occurred in local approved first-line bDMARD deliverability.*

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses			Introduction
Methods					
Study Design	4	Present key elements of study design early in the paper			Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Methods
Participants	6	*(a) Cohort study* - Give the		RECORD 6.1: The methods of study	Methods

		eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			Methods
Bias	9	Describe any efforts to address potential sources of bias			Discussion

Study size	10	Explain how the study size was arrived at			N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Methods
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Methods
Linkage		..		RECORD 12.3: State whether the	Methods

				study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			Results
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or			Results

		summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Results
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Results
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion

Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Submission information
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Submission information

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Comparative effectiveness of first-line biologic monotherapy use in rheumatoid arthritis: a retrospective analysis of the RECord-linkage On Rheumatic Disease study on health care administrative databases.

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	rheumatoid arthritis, biologics, drug persistence, conventional synthetic DMARDs

Research Article

Title

Comparative effectiveness of first-line biologic monotherapy use in rheumatoid arthritis: a retrospective analysis of the RECord-linkage On Rheumatic Disease study on health care administrative databases.

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Abstract

Objective

These analyses aim to comparatively evaluate the persistence on treatment of different biological disease-modifying antirheumatic drugs (bDMARDs) when administered in monotherapy compared to combination with conventional synthetic (cs)DMARDs in rheumatoid arthritis (RA) patients receiving first-line biologics.

Design

This is a retrospective observational study on Administrative Healthcare Databases.

Methods

Data were extracted from healthcare databases of the Lombardy Region, Italy (2004-2013), as a part of the RECord-linkage On Rheumatic Diseases (RECORD) study, on behalf of the Italian Society for Rheumatology (SIR). Analyses included RA patients starting first-line approved course of bDMARDs and evaluated drug survival by using Cox proportional hazard models. Results are presented as hazard ratios (HR) and 95%CI, crude and adjusted for pre-specified confounders (age, sex, disease duration, Charlson Comorbidity Index (CCI), previous infections, use of concomitant glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs)).

Results

4478 RA patients were included (17.84% monotherapy). Etanercept, adalimumab and infliximab were the most prescribed first-line biologics. bDMARD monotherapy was associated with longer disease duration, higher CCI, lower glucocorticoids and NSAIDs use. Compared to monotherapy, combination associated with a lower risk of failure (adjusted HR 0.79, 95%CI 0.72-0.88). Among monotherapies, considering etanercept as reference, adalimumab (1.28, 1.03-1.59) and infliximab (2.41, 1.85-3.15) had higher risk of failure. Concomitant methotrexate (0.78, 0.70-0.87),

leflunomide (0.80, 0.65-0.98), or csDMARD combinations (0.77, 0.68-0.87) reduced the risk of bDMARD withdrawal.

Conclusion

Adalimumab and infliximab monotherapies show lower retention rate compared with etanercept. The relatively small number of therapeutic courses different from TNF-inhibitors make more difficult to achieve conclusive results with other biologics. Concomitant methotrexate, leflunomide and csDMARD combination associate with longer survival on bDMARD. Our data confirm the effectiveness of the current practices in the choice of etanercept as first line anti-TNF monotherapy and strengthen the currently recommended use of bDMARDs in combination with csDMARDs.

Strengths and limitations of this study

- This study provides results from administrative databases, following a previous study with the complete validation of classification algorithms for the identification of patients with rheumatoid arthritis (RA) at the population level through healthcare administrative databases.
- This study, as expected by study design, has no loss to follow up and allows the analysis of a large sample of patients.
- Limitations of the RECORD study include the absence of specific disease clinical outcomes, in particular no information are available about disease activity and radiographic progression.

Introduction

Biological disease modifying antirheumatic drugs (bDMARDs) are recommended in association with non-biological (conventional synthetic) disease-modifying drugs (csDMARDs) in the treatment of rheumatoid arthritis (RA). As stated by recent updated 2016 EULAR recommendations for the management of RA[1], bDMARDs should be combined with a csDMARD because of a superior efficacy of combination therapy. Among bDMARDs, recommendations suggest using tocilizumab (TCZ) when combination is not possible. Not only methotrexate (MTX) is useful in combination therapy, but other csDMARDs can be also considered.

The better performance of bDMARD combination therapy with csDMARDs over bDMARD monotherapy has been clearly established both in terms of efficacy and retention rate. A recent meta-analysis of the Hazard Ratios (HRs) of bDMARDs discontinuation shows a 23% lower risk of drug withdrawal for any cause in patients treated also with csDMARDs[2]. A possible pharmacodynamic explanation is linked to an additive effect in the inhibitory profile of the combined drugs. In particular, differences between biologics exist and MTX plus adalimumab (ADA) inhibits more biological pathways compared to MTX plus TCZ, suggesting a synergistic effect of MTX in immunosuppression which differs across drugs[3]. A pharmacokinetic effect of incremental doses of MTX in enhancing serum concentrations of ADA was also observed[4]. Moreover, the immunogenicity of biologics, in terms of occurrence of anti-drug antibodies, is lower in combination therapy and MTX reduces the incidence of the appearance of such antibodies[5,6]. The effect of csDMARDs other than MTX in reducing immunogenicity of TNF-inhibitors (TNFi) is still unknown. TCZ and etanercept (ETA) share low immunogenicity[7,8]; MTX association did not influence the production of anti-TCZ[9] and anti-abatacept (ABA) autoantibodies and, when autoantibodies occur, they are not associated with adverse events or

discontinuation of therapy[10]. Reduction in disability and radiographic progression are also superior in combination regimens[11].

Limited data are available about the best biological treatment choice in real-life when a biologic monotherapy is necessary for biologic-naïve patients. In clinical practice, contraindications to MTX or early intolerance to csDMARDs are frequently observed, and clinicians need to start a biologic monotherapy in these cases; the result is that RA patients are treated with monotherapy nearby in one third or even more cases[12–16].

Differently from randomized controlled trials (RCTs), data from observational studies or registries explore the utilization of monotherapy in real-life clinical practice[2] and persistence in therapy is considered a good indirect and composite measure of effectiveness, safety and tolerability, reflecting the long-term impact on the course of the disease. Data of real-life overall persistence show that monoclonal TNFi are burdened by a higher risk of drug failure compared to ETA[2]. Limited data are available for non-TNFi.

Objective of this analysis was to assess, in RA patients receiving first-line approved biological therapy, the comparative effectiveness (expressed in terms of drug survival) of different bDMARDs when administered in monotherapy compared with combination therapy, accordingly to real-life clinical practice and in compliance with local regulatory approvals. Secondary objectives were to characterize features of patients starting monotherapy and to evaluate the specific effect of MTX combination therapy compared with other csDMARDs association regimens in determining persistence of bDMARD co-therapy.

To answer these questions, we took advantage by the RECord-linkage On Rheumatic Diseases (RECORD) dataset, including data from administrative health database (AHD) of the Lombardy

region (Italy), analysing bDMARDs and concurrent drug exposures of all the first courses of bDMARDs of RA patients between 2004 and 2013.

Materials and Methods

Study Design and Setting

This is a retrospective observational study on AHD of Lombardy Region, Italy (>10,000,000 inhabitants). Access to data was granted by the General Directorate of Health for the purpose of the RECORD study, a project promoted by the Italian Society for Rheumatology (SIR) aiming to set up a national surveillance system to monitor the health burden of rheumatic diseases in Italy using AHD. The protocol was approved by the ethical committee of the Pavia University Hospital. Data included were retrieved between 1st of January 2004 and 31st of December 2013.

Patient and Public involvement

This a retrospective study based on AHD; patients were not directly involved in the research.

Participants and variables

The design of the RECORD study includes a database population of patients with RA and 4 age and sex-matched controls from the general population. Patients with RA were identified through co-payment exemption code 006.714.0, based on its previously demonstrated high specificity (96.39%) and high sensitivity (77.08%) for RA[17], in line with other studies following a similar methodology[18,19].

Study population was defined among patients with RA and at least one delivery of first-line approved bDMARDs (abatacept (ABA), adalimumab (ADA), certolizumab (CTZ), etanercept (ETA), golimumab (GOL), infliximab (INF) and tocilizumab (TCZ)). Rituximab (RTX) was excluded due to the local limitation in first-line deliverability of this drug in RA patients. The exposure to non-steroidal anti-inflammatory drugs (NSAIDs), daily mean glucocorticoid (GC) dosage (expressed in terms of prednisone equivalent, mg per day) and to specific csDMARDs (MTX, Leflunomide (LFN),

Cyclosporine A (CYA), Hydroxychloroquine (HCQ) or Sulphasalazine (SSZ)) was defined by the drug delivery recorded in the administrative database.

Data included demographics (birth date, gender, death date or embarkment, drug delivery (Anatomic-Therapeutic Chemical, ATC) - code, date of drug delivery, quantity), exemptions (exemption code, date of exemption), outpatient services (code and date) and hospital discharge forms including information on beginning and end of hospitalization, International Classification of Disease, 9th revision, Clinical Modification (ICD-9-CM) diagnoses and Disease Related Group. Previous bacterial infections were considered if hospitalization for bacterial infection or an antibiotic treatment course of over 14 days occurred in the previous year[20].

Statistical methods

The primary outcome was persistence with first-line bDMARD, which was defined as the length of time between drug delivery plus drug coverage. A patient was considered exposed to a specific treatment from the first prescription of drug until the last one plus 6 months, in order to consider the coverage period of drug also after its withdrawal, or until the first prescription of the subsequent drug. Censoring was defined at treatment stop date plus drug coverage or until the start of a new bDMARD, death or at the end of established follow-up, whichever came first. Drug persistence in bDMARD therapy was compared using Cox proportional Hazard models. Results were presented as HR and 95%CI, crude and adjusted for pre-specified confounders (sex, age, disease duration, Charlson Comorbidity Index (CCI)[21], concomitant use of NSAIDs, GCs average dosage and previous bacterial infections). A secondary analysis, focused on the role of each associated csDMARD in bDMARD persistence, was analyzed by the same mechanism (firstly considering combination biologics as a whole and then investigating the interaction between different csDMARDs and each bDMARD). A sensitivity analysis was performed to investigate if different periods of bDMARDs prescription could have influenced persistence data (a distinction

was made before and after 31st December 2009, according to changes occurred in local bDMARDs deliverability).

All the analyses were performed using the Stata11 software (STATA Corporation, College Station, Texas, USA) and R statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Results

Study population and Descriptive Data

A total of 4478 RA patients who had their first-line bDMARD delivery were included (13728 person/time). 3472 were women (77.53 %); mean age (standard deviation, SD) at bDMARD exposure was 55.48 (12.69) years with a modal disease duration of over five years. No missing data nor lost to follow-up were recorded, nor expected by design. A mean (SD) CCI of 1.16 (0.48) was observed (Table 1).

bDMARD monotherapy was administered to 799 patients (17.84%) while 3679 (82.16%) experienced csDMARDs association. Most prescribed bDMARDs were ETA (1787 patients, 39.91%), ADA (1143, 25.52%) and INF (861, 19.23%). ETA was the most prescribed drug out of monotherapy (385 patients, 48.19%) and in combination group (1402 patients, 38.11%) (Table 2).

Among concomitant csDMARD therapy, MTX was the most commonly prescribed (2297 patients had only concurrent MTX, 62.44%); 223 only concurrent LFN (6.06%), 151 concurrent HCQ (4.10%), 43 SSZ (1.17%), 41 CYA (1.11%). 924 patients (25.12%) experienced a combination of different csDMARDs; in this group a total of 827 patients received MTX, 254 LFN, 131 SSZ, 619 HCQ, 116 CYA.

451 bDMARD monotherapies were started before 31st December 2009 (252 ETA, 136 ADA, 62 INF, 1 ABA, no TCZ, CTZ and GOL) and 348 after 1st January 2010 (133 ETA, 65 ADA, 47 TCZ, 33 ABA, 30 CTZ, 21 GOL and 19 INF).

Factors influencing monotherapy

Monotherapy was associated with longer disease duration, a higher CCI (in particular hepatic and renal disease and heart failure), lower use of GCs and NSAIDs (Table 1).

Table 1. Clinical and demographic features of the study population including 4478 RA patients and their distribution in bDMARDs mono- and combination therapy.

Demographic characteristics	*Study population*	*Monotherapy (N. 799)*	*Combination (N 3679)*	*p*
Mean age (SD, years)	55.48 (12.69)	54.90 (12.97)	55.61 (12.62)	0.136
Female, n (%)	3472 (77.53)	614 (76.85)	2858 (77.68)	0.607
Clinical characteristics				
Disease duration N (%)				
• < 1 years	1028 (22.96)	153 (19.15)	875 (23.78)	<0.001
• > 1 to ≤ 2 years	1106 (24.7)	188 (23.53)	918 (24.95)	
• ≥ 3 to ≤ 5 years	1064 (23.76)	171 (21.40)	893 (24.27)	
• > 5 years	1280 (28.58)	287 (35.92)	993 (26.99)	
Number of comorbidities = 0 N (%)	3941 (88.01)	683 (85.48)	3258 (88.56)	0.004
Number of comorbidities = 1 N (%)	416 (9.29)	80 (10.01)	336 (9.13)	
Number of comorbidities = 2 N (%)	105 (2.34)	30 (3.75)	75 (2.04)	
Number of comorbidities > = 3 N (%)	16 (0.36)	6 (0.75)	10 (0.27)	
Charlson Comorbidity Index *, Mean (SD)	1.16 (0.48)	1.22 (0.60)	1.15 (0.45)	0.009
CHD, N (%)	66 (1.47)	16 (2.00)	50 (1.36)	0.193
Heart Failure, N (%)	12 (0.27)	5 (0.63)	7 (0.19)	0.047
Vascular Pathology, N (%)	10 (0.22)	4 (0.50)	6 (0.16)	0.086
Dementia, N (%)	1 (0.02)	1 (0.13)	0 (0.00)	0.178
COPD, N (%)	49 (1.09)	11 (1.38)	38 (1.03)	0.451
Mild Hepatic disease **, N (%)	73 (1.63)	24 (3.00)	49 (1.33)	0.002
Diabetes, N (%)	276 (6.16)	41 (5.13)	235 (6.39)	0.195
Renal Disease, N (%)	32 (0.71)	18 (2.25)	14 (0.38)	<0.001
Neoplasm **, N (%)	67 (1.50)	16 (2.00)	51 (1.39)	0.198
Leukemia / Lymphoma, N (%)	1 (0.02)	1 (0.13)	0 (0.00)	0.178
Previous Infections, N (%)	822 (18.36)	140 (17.52)	682 (18.54)	0.501
Concomitant NSAIDs, N (%)	3386 (75.61)	485 (60.70)	2901 (78.85)	<0.001
Concomitant GCs, N (%)	3045 (68.00)	428 (53.57)	2617 (71.13)	<0.001
GCs dose (mg/day), mean (SD)	2.23 (3.08)	1.85 (3.32)	2.31 (3.01)	<0.001

CHD: Coronary Heart Disease; COPD: Chronic Obstructive Pulmonary Disease; AIDS: Acquired Immunodeficiency Syndrome.
** Diabetes with end-organ damage, AIDS, cerebrovascular disease, peptic ulcer and hemiplegia are not shown due to absence of cases in monotherapy group.*
*** Severe hepatic disease and metastatic neoplasms are not shown due to absence of cases in both groups.*

Table 2. Distribution of different bDMARDs in mono- and combination therapy with csDMARDs

bDMARDS	*Study population*	*Monotherapy (N. 799)*	*Combination (N 3679)*
ABA N (%)	189 (4.22)	34 (4.26)	155 (4.21)
ADA N (%)	1143 (25.52)	201 (25.16)	942 (25.60)
CTZ N (%)	156 (3.48)	30 (3.75)	126 (3.42)
ETA N (%)	1787 (39.91)	385 (48.19)	1402 (38.11)
GOL N (%)	151 (3.37)	21 (2.63)	130 (3.53)
INF N (%)	861 (19.23)	81 (10.14)	780 (21.20)
TCZ N (%)	191 (4.27)	47 (5.88)	144 (3.91)

Risk of bDMARD failure

Compared to monotherapy, combination with at least one csDMARD was associated with a lower risk of drug failure (crude HR 0.77, 95%CI 0.69-0.85; adjusted HR 0.79, 95%CI 0.72-0.88). Among patients in bDMARD-monotherapy, considering ETA as reference, the adjusted HR for bDMARD failure was 1.28 for ADA (95%CI 1.03-1.59) and 2.41 for INF (95%CI 1.85-3.15) (Figure 1); ABA monotherapy was associated with a reduced - but not statistically significant - risk of failure, while TCZ was almost equal to ETA. Otherwise, among combination therapies, only INF was significantly inferior compared with ETA monotherapy. The risk of failure evaluated for the other bDMARDs was not statistically different from ETA monotherapy.

Influence of different csDMARDs in persistence in bDMARD treatment

Considering specific combination therapy and taking bDMARD monotherapy as reference, concurrent csDMARDs significantly reduced the risk of bDMARD withdrawal (adjusted HR 0.78 for MTX alone, 95%CI 0.70-0.87; HR 0.80 for LFN alone, 95%CI 0.65-0.98; HR 0.77 for combination of different csDMARDs, 95%CI 0.68-0.87) (Figure 2), while no statistical significant improvement in drug survival was observed for SSZ, HCQ or CYA when used as the single associated csDMARD.

The analysis of different csDMARDs in determining persistence of different bDMARD treatment showed that MTX alone or in combination with other csDMARDs positively influenced persistence in INF treatment, while other associations between csDMARDs and bDMARDs did not significantly modify the concomitant biologic drug survival.

Sensitivity analysis

After stratification in different periods of time (before and after 31st December 2009) an increase in the previous reported risk of drug failure for INF was observed (HR 2.72, 95%CI 1.51-4.90). The risk of ADA failure remains elevated compared to ETA monotherapy, but differences according to the time period were no longer significant (HR 1.17, 95%CI 0.70-1.96); the risk of failure for other

bDMARDs remains not significantly different from ETA (Supplementary file 1). A sub-analysis of the patients receiving ADA monotherapy after 1st January 2010 showed that in this group a proportional higher number of males was present (p=0.004), with longer disease duration (p<0.001) and higher CCI (p=0.018).

Discussion

Using bDMARDs as monotherapy in clinical settings is a common practice for RA patients and recognised by health authorities although current guidelines recommend combining them with csDMARDs. The aims of this study were to describe persistence and factors associated with starting biologic monotherapy in a real-world setting. In our study, monotherapy was common and observed in approximately 1 out of 5 biologic-naive patients with RA initiating a biologic agent (17.8%). In previous biologics registries and claims database studies, 12–39% of patients were taking biologics as monotherapy[22–24].

From a practical perspective, it seems even more important to investigate those factors which may drive prescribing monotherapy. Indeed, bDMARDs monotherapy could be representative of a subgroup of patients with a more difficult disease management[25]. It has been reported that older patients, with longer disease duration and multiple comorbidities, lower body mass index (BMI) and higher disease activity show higher probability to undergo monotherapy[16,22,25,26]. Concomitant use of glucocorticoids predicts higher bDMARD discontinuation, reflecting a much severe course of the disease[2,23]. Accordingly, in our retrospective study based on AHD, we have observed a significant association between monotherapy and longer disease duration and a higher number of comorbidities. As expected, hepatic and renal diseases were the most limiting factors for csDMARDs association. NSAIDs and GCs were negatively associated with monotherapy, likely reflecting contraindication to these drugs due to concomitant comorbidities.

As demonstrated by the majority of published real-life studies and RCTs, our study confirms that bDMARD risk of failure is significantly lower in combination with csDMARDs (21% lower risk of drug withdrawal compared to monotherapy). Concerning monotherapy, in a Swiss study of retention rate which analyses data from Swiss Clinical Quality Management Registry (SCQM-RA) between 2004 and 2013[25], 27% of all biologics therapeutic courses was initiated as

monotherapy (the higher percentage of monotherapy was for CTZ with 46%; 35% ETA; 35% TCZ; 29% ABA; 26% ADA; 23% RTX; 17% GOL and 14% INF) and a further 13% experienced a transient phase of monotherapy overtime; discontinuation of bDMARD occurred in 63% (1545/2453) and the adjusted HR for discontinuation of biologic monotherapy versus combination was 1.15 (95%CI 1.03-1.30, p=0.018), although differences between the two groups were relatively modest. Treatment failure was influenced not only by the type of bDMARD but even by gender, number of previous bDMARDs, year of initiation of the receiving drug, seropositivity, disease duration and activity. TNFi strongly impact these data, being historically the first bDMARD entered in clinical practice and accounting for about 80% of therapeutic courses; therefore, conclusive results are still lacking. Overall, the type of bDMARD is certainly one of the most important factors influencing persistence, and INF monotherapy is burdened by the higher rate of withdrawal[2,23,27]. Globally, monoclonal antibodies against TNF-alfa share higher discontinuation compared to ETA[2,28]; whether the global higher immunogenicity of monoclonal antibodies is strictly responsible for this difference is still matter of debate. In an observational study, Kristensen et al.[29] stand out a higher adherence in first-line ETA-treated patients compared to INF; concomitant MTX was associated with better persistence in both groups but significantly higher for ETA. In a 12-years retention rate study of first-line TNFi, Favalli et al.[30] demonstrated a higher risk of drug failure for ADA (HR 2.89, 95%CI 2.2-3.78) and INF (HR 2.56, 95%CI 1.92-3.4) compared to ETA, similarly to what is reported by a French multicentric study by Frazier-Mironer[31] and the GISEA registry[32]; MTX-users in combination with biologic shared higher retention rate compared with TNFi monotherapy (HR 1.48, 95%CI 1.18-1.86). Jorgensen et al.[23] analysed 775 pts in the Danish registry and showed that persistence in monotherapy was significantly higher for all biologics compared to INF (HR of withdrawal 2.53 for INF compared to other bDMARDs, 95%CI 1.70-3.77, p <0.001) and these features were indipendent of the number of previous biologics. In German RABBIT registry, a longer persistence was found in combination therapy with TNFi but remission

rates were not significantly different from monotherapy group[14]. The south Swedish SSATG registry[33] evaluated differences in biologics monotherapy persistence in different biologics courses over 6 years and highlighted a significant difference among bDMARDs with highest retention rates observed for RTX and ETA. In RADIUS registry[34], which analyzed different efficacy between ETA, INF and csDMARDs therapy, patients receiving either ETA plus MTX (adjusted OR 1.29, 95%CI 1.09-1.52, p<0,01) or ETA monotherapy (OR 1.23, 95% CI 1.02-1.47, p<0,05) were more likely to achieve a modified ACR20-response at 12 months than patients receiving MTX alone, INF plus MTX or INF alone; persistence in therapy however was higher for INF plus MTX (71% of INF group persisted in therapy after 12 months; versus 69% of ETA monotherapy, 67% INF alone and 61% ETA plus MTX); noteworthy cost of the therapy was claimed as a significant cause of discontinuation of biologic therapy in this registry (up to 6% of ETA monotherapy changed treatment due to high costs). The ACT-iON observational study[35] explored different persistence rates among first-line TNFi and TCZ and showed a better persistence for TCZ compared to TNFi as a whole; a comparison between first-line monotherapies was not possible due to the low number of cases. Our data are in keeping with current literature and show a lower persistence for first-line monoclonal TNFi (ADA and INF) monotherapy compared with ETA monotherapy, suggesting that these bDMARDs should be avoided when a TNFi monotherapy is thought to be necessary.

Data from RTCs confirm this tendency among TNFi, either in terms of retention rate as well for radiological outcomes, but long term head-to-head comparative trials among different bDMARDs specifically designed to test this outcome are lacking. With regard to non-TNFi, data about a real superiority of combination therapy compared to monotherapy are controversial[7,26]. A pan-European analysis of registries including nearby 3400 pts showed that retention of ABA was not influenced by csDMARDs co-therapy[7]. TCZ has gained the reputation to be the best bDMARD to utilize in monotherapy and the only one with a satisfactory durability[12,13,36] and cost-

effectiveness[37]. However, also for this drug, association strategy has demonstrated to be useful in clinical trials giving some advantages when compared with monotherapy. In ACT-RAY trial, after 2 years, a difference in radiographic progression was observed favoring combination regimen with MTX[38] and, in a recent post-hoc sub-analysis of ACT-SURE study, concomitant csDMARDs helped to achieve low disease activity earlier than in TCZ monotherapy[39], similarly to what demonstrated by Kaneko et al. in SURPRISE study[40]. Conversely, other studies did not show particular advantages in terms of clinical efficacy of TCZ combination therapy over monotherapy[41,42]. In ADACTA study[43] TCZ monotherapy reduced significantly disease activity score (DAS) and Clinical Disease Activity Index (CDAI) compared to ADA monotherapy after 24 weeks, in a head-to-head comparison between monotherapies. Our study confirms a similar persistence rate between non-TNFi monotherapy compared to combination, but the small size of our sample and the calendar-period of the analysis does not allow a conclusive remark.

Our data show that either MTX or LFN or combination of different csDMARDs significantly increase bDMARDs persistence rate, while CYA is associated with a higher (but not significant) rate of drug failure. Previous reports on the benefits of combining different csDMARDs with bDMARDs have shown contrasting results; Soliman et al.[16] explored the role of different csDMARDs intervention in biological persistence in a real-life study which evaluated persistence in over 10,000 pts from a British registry and stated that MTX combination was linked to a better persistence of the first TNFi when compared to no csDMARDs, LFN or SSZ but the best overall persistence was seen among pts receiving TNFi in combination to MTX and either SSZ or HCQ or both, in line with our results. Similarly, Manders et al. found a similar persistence rate in TNFi plus MTX group compared to TNFi plus MTX plus others[44]. De Stefano et al.[45] reported a similar efficacy and safety profile for TNFi combined with either MTX or LFN in Early RA, but univocal data for LFN combination to bDMARDs are lacking and limited by the high number of associations with INF[46].

Conversely, Kristensen et al.[29] demonstrated that concomitant MTX, but not other csDMARDs, was associated with a better persistence with first-line ETA or INF therapy, but significantly higher for ETA. A positive influence in terms of efficacy has been observed for LFN combined with RTX in GERINIS study[47] and in CERERRA collaboration[48].

When stratifying by calendar year - subclasses, after the introduction of other bDMARDs in current recommended therapeutic approach, the risk of failure for INF monotherapy slightly increased, while ADA monotherapy became not statistically different from ETA. Higher number of comorbidities and longer disease duration in this subgroup could reflect the selection of a particular subset of patients for whom an acceptance of a sub-optimal control of disease activity has been made, despite a real efficacy of the drug. Afterwards, the reduction of the sample size after this stratification could have influenced the results as well as the prescription attitude of bDMARDs might have changed during the period of analysis. In fact, as shown by literature[2,25], the year of treatment could have influenced bDMARD retention rate, since rheumatologists are more prone to change biologics if more alternatives are available[27], although data about this issue are controversial[49].

Our study has some limitations. The different burden of prescribed bDMARDs (being ETA, ADA and INF the most prescribed ones) could have influenced our results; to this regard, GOL, CTZ and non-TNFi associated with a lower prescription rate and RTX was excluded due to the local limitation in first-line deliverability. This limitation makes conclusions not generalizable for all biological agents. We adjusted for pre-specified confounders but confounding of unmeasured factors could not be excluded (50), for example other comorbidities different from those included in CCI, previous csDMARDs treatment history, changed treatment behaviour overtime with different GCs and NSAIDs utilization schemes or specific musculoskeletal disease or patients-related characteristics (radiological features, concomitant osteoarthritis, crystal arthropathies or fibromyalgia).

Furthermore, the design of the study could not differentiate between patients starting monotherapy “ab initio” and those reaching such monotherapy by a “step-down” process; despite this behavior accounts for only a small proportion[25], the overall prevalence could have been under-recognized due to specific design of trials and “real-life” databases[16]; anyway, characterizing such a population was out of the scope of our study which focuses only on the first group (“ab initio” monotherapies). Other limitations are intrinsic in the AHD-based design of the study, in particular lack of control of data collected for non-clinical purposes and misclassification biases; furthermore clinical outcomes are lacking (absence of disease activity and radiological outcome data; specific causes of bDMARD failure or monotherapy prescription, such as patients’ or physicians’ preferences[22]; possible alternative therapeutic schemes, including spacing of the bDMARD scheduled administration; different dosages of csDMARDs co-therapy)[50]. AHD reflect drug dispensing instead that the exact specialists’ “prescription” habit or the real patients’ adherence, thus resulting in a difference between the rate of prescribed monotherapies and the rate of drug acquisition and use. Anyway, AHD are commonly considered a good instrument to estimate drug prescription and exposure[51] and our data are in line with results from registries regarding monotherapy use in RA.

However, the RECORD study has some relevant strengths: its large sample size, allowing the examination of the effect of concomitant bDMARDs and csDMARDs, and the completeness of data without loss at follow-up. This is, to our knowledge, the first AHD-based study investigating different persistence rates in first-line biological monotherapies combining all bDMARDs approved as “first-line” treatment.

In conclusion, our study supports the currently recommended use of bDMARDs in combination with csDMARDs, underlining a higher risk of drug withdrawal for TNFi monotherapy compared with combination and suggesting that, among bDMARDs, ETA should be preferred over INF - and

to lesser extent ADA - when a first-line monotherapy is necessary. Despite univocal conclusions are not possible for non-TNFi, our results strengthen the positive influence of MTX, LFN or combination of csDMARDs in improving bDMARDs persistence.

Figure Legends

Figure 1

Crude and adjusted HR and 95%CI for bDMARD failure when administered in first-line monotherapy and in combination with csDMARDs.

Figure 2

Crude and adjusted HR and 95%CI for different csDMARDs in determining the risk of fist-line bDMARD failure.

Competing interests:

E. Silvagni; G. Carrara; A. Zanetti; C.A. Scirè: none to declare. A. Bortoluzzi: Sanofi, Alfa-Wasserman. M. Govoni: Pfizer, Abbvie, MSD, Roche, BMS, Sanofi, Lilly, Novartis, Celgene: fees for sponsored lectures and/or participation in advisory boards.

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No additional information are available.

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Authorship Criteria:

Substantial contributions to study conception and design: ES, AB, GC, AZ, MG, CAS

Substantial contributions to acquisition of data: GC, ES, AZ, CAS

Substantial contributions to analysis and interpretation of data: ES, AB, GC, CAS

Drafting the article or revising it critically for important intellectual content: ES, AB, GC, AZ, MG, CAS

Final approval of the version of the article to be published: ES, AB, GC, AZ, MG, CAS

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: ES, AB, GC, AZ, MG, CAS

No other potential author who fulfils the ICMJE Recommendations criteria has been excluded as an author.

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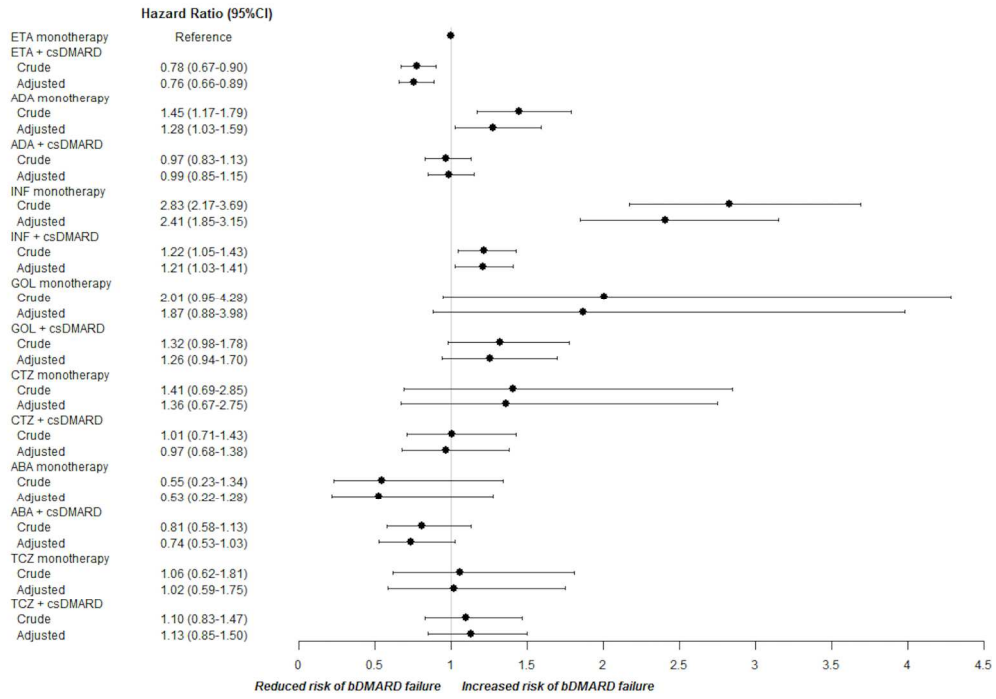

Figure 1
Crude and adjusted HR and 95%CI for bDMARD failure when administered in first-line monotherapy and in combination with csDMARDs.

163x114mm (300 x 300 DPI)

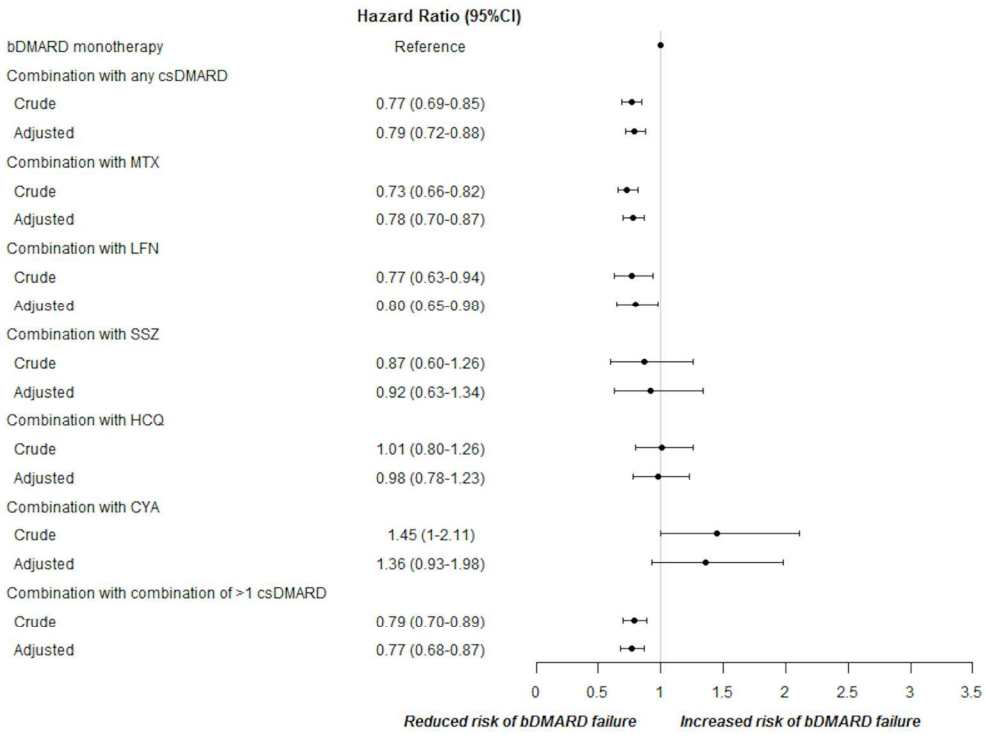

Figure 2
Crude and adjusted HR and 95%CI for different csDMARDs in determining the risk of fist-line bDMARD failure.

152x114mm (300 x 300 DPI)

Supplementary file 1. Risk of drug failure of different bDMARDs monotherapy before and after 31st december 2009.

bDMARD monotherapy	*Adjusted HR (95%CI) before 31st december 2009*	*p*	*Adjusted HR (95%CI) after 1st January 2010*	*p*
ETA monotherapy (385 patients)	1 (ref)		1 (ref)	
ADA monotherapy (201 patients)	1.40 (1.09 – 1.78)	0.008	1.17 (0.70-1.96)	0.554
INF monotherapy (81 patients)	2.20 (1.59 – 3.05)	<0.001	2.72 (1.51 – 4.90)	0.001
GOL monotherapy (21 patients)	*Not applicable**		1.38 (0.60 – 3.18)	0.447
CTZ monotherapy (30 patients)	*Not applicable**		1.08 (0.51 – 2.29)	0.843
ABA monotherapy (34 patients)	*Not applicable**		0.46 (0.18 – 1.15)	0.097
TCZ monotherapy (47 patients)	*Not applicable**		0.82 (0.45 – 1.48)	0.504

** Not applicable: based on the changes occurred in local approved first-line bDMARD deliverability.*

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title, Abstract, page 1-2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction, page 5-6
Objectives	3	State specific objectives, including any prespecified hypotheses			Introduction, page 6
Methods					
Study Design	4	Present key elements of study design early in the paper			Methods, page 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment,			Methods, page 8

		exposure, follow-up, and data collection			
Participants	6	a) Cohort study - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants (b) Cohort study - For matched studies, give matching criteria and number of exposed and unexposed Case-control study - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Methods, page 8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods, page 9
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment			Methods, page 8-9

		(measurement). Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias			Discussion, page 20-21
Study size	10	Explain how the study size was arrived at			N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Methods, page 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) Cohort study - If applicable, explain how loss to follow-up was addressed Case-control study - If applicable, explain how matching of cases and controls was addressed Cross-sectional study - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Methods, page 9

Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Methods, page 8
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods, page 8
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (i.e., study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results, page 11
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest			Results, page 11

		(c) Cohort study - summarise follow-up time (e.g., average and total amount)			
Outcome data	15	Cohort study - Report numbers of outcome events or summary measures over time Case-control study - Report numbers in each exposure category, or summary measures of exposure Cross-sectional study - Report numbers of outcome events or summary measures			Results, page 14
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Results, page 14
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Results, page 11-14
Discussion					
Key results	18	Summarise key results with			Discussion, page 16

		reference to study objectives			
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion, page 20-21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion, page 16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion, page 16-22
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Submission information
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Submission information

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLoS Medicine 2015.