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Risk of hospitalization for heart failure in rheumatoid arthritis patients treated with etanercept and abatacept

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Abstract

To estimate biologic influence on heart failure (HF) risk in rheumatoid arthritis. Retrospective cohort (RECORD Study of Italian Society for Rheumatology) study on administrative healthcare databases. We identified 2527 patients treated with either etanercept ($n=1690$) or abatacept ($n=837$). HF incidence rate was higher in the abatacept cohort than in the etanercept cohort with a 2.38 (95% CI 1.08–5.27) crude competing risk HR (SHR) for abatacept of developing HF, not confirmed after adjustment for prespecified confounders (SHR 1.43; 95% CI 0.51–3.98). Abatacept, compared to etanercept, is prescribed to patients with a worse cardiovascular profile but does not increase the risk of developing HF, when confounding factors are accounted for.

Keywords Cardiovascular · Epidemiology · DMARDs · Biologic

Introduction

Chronic inflammation is associated with cardiovascular (CV) risk beyond traditional factors [1], and CV disease remains the most common death cause in rheumatoid arthritis (RA) [2]. Heart failure (HF) has been reported to occur as high as 24% in RA populations with high disease activity, compared to 6% in controls [3].

Tumor necrosis factor (TNF)-α and pro-inflammatory cytokines, i.e., interleukin(IL-6) and IL-1β, are associated with HF [4]. As TNFα levels are increased in HF [5], the blockade of this inflammatory pathway may reduce the incidence of HF in RA; however, data from clinical trials are conflicting, with most of the registrative studies reporting no beneficial effects and a possible worsening of HF, leading to anti-TNFα contraindication in HF within New York Heart Association (NYHA) classes III–IV (moderate and severe) [6]. Longer observational studies have been conducted on almost all anti-TNFα, including etanercept (ETN), with inconsistent results [7, 8]. Biologics with different mechanisms of action, rituximab (anti-CD20), tocilizumab (anti-IL6) and abatacept (ABA) (anti-CTLA4) showed no reduction of the risk of developing HF and other CV events compared to the RA population treated with traditional disease modifying antirheumatic drugs (DMARDs) or anti-TNFα [9, 10].

We moved from recent data supporting the role of CTLA4 on the development of hypertension-induced HF [11] and herein estimate the influence of treatment with ETN and ABA on HF risk.

in RA patients in a real-life setting.

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Methods

Study design

This is a retrospective cohort study on the administrative healthcare databases (AHD) of the Lombardia Region, Italy, accounting for a 10 million population. The study design and report comply with the RECORD statement.

Data were retrieved by RECord linkage from AHD: demographics, pharmacy, copayment exemption for chronic diseases, outpatient services, hospital discharge forms (HDF). The following variables were extracted: birth date, sex, death or embankment date, anatomic-therapeutic chemical (ATC) classification numbers, date of prescription and quantity of drug for each prescription, exemption codes, date of exemption, codes and dates of each outpatient services and International Classification of Diseases (ICD)-9-CM diagnoses, Diagnostic-Related Groups (DRG), and start–end dates for every hospitalization, for the period between 1st of January 2010 and 31st of December 2013. The access to the data was granted by the General Directorate of Health for the RECord-linkage On Rheumatic Diseases (RECORD) study protocol of analysis, in accordance with ethical requirements, and the RECORD protocol approved by the ethical committee of the University hospital of Pavia, Italy (deliberation of 12/03/2012). No patient's consent was required.

Case finding, treatment exposure, and outcomes

Patients with RA were identified through a validated algorithm [12]. The exposure to specific drugs was estimated by the drug delivery: patients with at least one ABA delivery entered in ABA cohort, patients with at least one ETN prescription entered in ETN cohort. A patient was considered exposed to the treatment from the first prescription until the last one plus six months, to consider the coverage period of drug also after its withdrawal. Temporary stops were allowed, regardless of their duration. Hospitalization/death for HF during the exposition period were evaluated using HDF based on previously validated relevant ICD-9-CM codes and DRG [13]. Comorbidities (e.g., hypertension, myocardial infarction, renal failure, diabetes, and dyslipidemia) were identified using corresponding ICD-9-CM codes form exemptions and HDF, as well as non-steroidal anti-inflammatory drugs (NSAIDs), steroids and previous biologics deliveries, using ATC codes. Death was recorded and accounted as a competing risk in the statistical analysis.

Statistical methods

The association between exposure to ETN or ABA and hospitalization/death for HF was assessed by Cox regression and survival models for competing risks (i.e., death). Results were presented as hazard ratios (HR) and 95% confidence intervals (CI), crude and adjusted for prespecified confounders (sex, age, disease duration, use of methotrexate (MTX), corticosteroids, NSAIDs, number of previous biologics, hypertension, dyslipidemia, diabetes, previous myocardial infarction and renal failure). Analyses were performed using STATA13 software package (StataCorp. 2013. College Station, TX, USA).

Results

We identified 2527 patients with RA, of which 1,690 treated with ETN and 837 with ABA. The demographic and therapeutic features of patients are reported in Table 1. RA cases enrolled in the ABA cohort, compared to ETN, are more frequently women (82.2% vs. 71.1%, $p<0.001$), older (mean age 59 year vs. 55, $p<0.001$), with longer disease duration (> 3 years in 80.6% vs. 67.1%, $p<0.001$), use more corticosteroids (72.5% vs. 60.5%, $p<0.001$) have been previously treated with biologics (median 1 vs. 0, $p<0.001$), have a higher prevalence of arterial hypertension (24.5% vs. 18.7%, $p=0.001$), and dyslipidemia (19.4% vs.14.4%, $p=0.002$). No significant differences are found between groups in terms of concomitant use of NSAIDs and MTX, diagnosis of diabetes, previous myocardial infarction and renal failure. Death was observed in 76 cases, 46 treated with ETN and 30 with ABA ($p=0.282$).

HF occurred in 12/837 patients treated with ABA, and in 13/1690 with ETN, with higher crude incidence rates in the ABA cohort compared to ETN, with the former being 7.23 and the latter 2.96 (Table 2).

The crude HR for HF development in the ABA group compared to ETN was HR of 2.42 (1.10–5.34, $p=0.028$), and adjusted for prespecified confounders was 1.42(0.59–3.45, $p=0.436$). The competing risk analysis for HF development (SHF) confirmed the observations, with a crude SHR of 2.38 (1.08–5.27, $p=0.032$), and an adjusted SHR of 1.43 (0.51–3.98, $p=0.497$) (Table 3).

Discussion

RA is associated with an increased CV risk and HF represents a major comorbidity linked to the CV risk of mortality associated with chronic inflammation [2]. Chronic

Table 1 Demographic and clinical characteristics of patients with RA included in our study

	All patients ($n=2527$)	Etanercept ($n=1690$)	Abatacept ($n=837$)	p value
Female, n (%)	1.889 (74.8)	1.201 (71.1)	688 (82.2)	<0.001
Age mean, years (SD)	56 (13)	55 (13)	59 (12)	<0.001
Disease duration < 1 year, n (%)	215 (8.5)	166 (9.8)	49 (5.9)	<0.001
Disease duration 1–2 years, n (%)	503 (19.9)	390 (23.1)	113 (13.5)	
Disease duration > 3 years, n (%)	1.809 (71.6)	1.134 (67.1)	675 (80.6)	
Previous biologic therapy* median, (IQR)	0 (0–1)	0 (0–1)	1 (0–2)	<0.001
NSAIDs use, n (%)	1.760 (69.7)	1.169 (69.2)	591 (70.6)	0.459
MTX use, n (%)	1.508 (59.7)	996 (58.9)	512 (61.2)	0.281
Oral steroids use, n (%)	1.629 (64.5)	1.022 (60.5)	607 (72.5)	<0.001
Preexisting hypertension, n (%)	521 (20.6)	316 (18.7)	205 (24.5)	0.001
Preexisting diabetes, n (%)	205 (8.1)	132 (7.8)	73 (8.7)	0.430
Preexisting dyslipidemia, n (%)	406 (16.1)	244 (14.4)	162 (19.4)	0.002
Preexisting myocardial infarction, n (%)	59 (2.3)	35 (2.1)	24 (2.9)	0.212
Preexisting renal failure, n (%)	17 (0.7)	12 (0.7)	5 (0.6)	0.744

Table 2 Incident cases of heart failure in patients with rheumatoid arthritis treated with etanercept (ETN) and abatacept (ABA)

Cohort	Cases	Crude incidence rate (×1000 person–years)
ETN 4390 person–years	13	2.96 (1.72–5.10)
ABA 1659 person–years	12	7.23 (4.11–12.74)

inflammation plays a role in the development of HF, through a modulation of the vascular tone and integrity associated with coronary atherosclerosis and myocardial infarction, modifying vascular compliance and endothelial function, and causing subclinical myocardial fibrosis and heart dysfunction. High TNFα levels are associated with HF and left ventricular dysfunction; however, prior studies in RA showed controversial effects of anti-TNFα on the risk to develop HF [8]. The adaptive immune system is responsible for the sustenance of chronic inflammation, particularly through T cells. Until recently, the link between T cells and HF had not been clearly elucidated, yet recent studies have shown a pivotal role in HF, as T-cell infiltration in the left ventricle negatively contributes to HF progression, through the induction of cardiac fibrosis [11, 14]. In this view, the reduction of the T-cell infiltrate could represent a new target in HF. ABA inhibits the co-stimulatory pathways between antigen presenting cells and T cells, thus preventing the full activation of the latter. It may thus represent a possible treatment to reduce HF risk, as recent experimental data have confirmed [11]. However, clinical data on ABA and other biologics with different mechanisms of action are limited, and need to be further investigated [9].

Our findings show that, when analyzing a large real-life series of RA patients, those treated with ABA have signs of a more severe disease, as illustrated by the higher use of steroids, and increased number of previous biologic, and suffer from more CV comorbidities, i.e., hypertension and dyslipidemia, compared to those receiving ETN, confirming that ABA, due to its good safety profile [15], is used to treat patients at high risk or as a second/third-line option. We assume that the increased incidence rate of HF observed in the ABA cohort is mainly due to the preexisting increased CV risk profile of patients, and not caused by the biologic agent, as our results show no significant difference for HF between treatments, when adjusting for confounders that are unbalanced between treatment groups.

The strengths of our study include the large number of patients analyzed, which allowed us to estimate the risk of development of a relatively rare event such as HF in a large unselected population of patients with RA being followed at

Table 3 Competing risk analysis for heart failure development in patients with rheumatoid arthritis treated with abatacept (ABA) using ETN as reference

ETN reference	SHR for HF competing risk death	95% CI	p value
Crude	2.38	1.08–5.27	0.032
Adjusted for age, sex, disease duration	1.84	0.83–4.08	0.137
Adjusted for age, sex, disease duration, concomitant medications and comorbidities	1.43	0.51–3.98	0.497

different rheumatology centers. Second, through the use of a validated algorithm, we included virtually all patients treated with ABA and ETN in the period between 2010 and 2013 in our region, accounting for high sensitivity and specificity.

We acknowledge that our study has limitations in the possible underestimation of the risk of HF since only hospitalized cases were included, with no difference between severity and treatment due to the research approach. Moreover, the identification of a limited number of HF cases may account for the low power in identifying minor but still clinically significant risk differences in the adjusted analyses. Further, our approach based on large administrative databases does not provide patient's clinimetrics, such as disease activity scores (DAS28), or laboratory values, such as C-reactive protein, although we considered the use of glucocorticoids and NSAIDs as proxies of a more active disease, as shown in previous works [16–18]. Furthermore, we considered corticosteroid use as a confounding factor increasing CV risk [19], as shown by, but it was reported that low-dose corticosteroids do not increase the rate of CV events [20]. Ultimately, we could not account for all possible confounding factors, and some residuals may still overestimate the risk of HF in ABA cohort.

These findings have several clinical implications, as we observed that ABA did not increase the risk of HF, while may be a targeted therapy for selected high-risk patients. Further, early treatment of RA could revert this increased inflammatory burden and prevent its negative effects reducing mortality.

In conclusion, ABA was administered between 2010 and 2013 to patients with RA with a more severe disease and more metabolic and cardiovascular comorbidities compared to those treated with ETN; in this population, the HF incidence rate associated with ABA is higher than ETN, but when adjusting for confounding factors the HF risks associated with ABA and ETN do not differ significantly.

Author contributions EG, GC, AB, CS, CAS, MK, GC designed the idea, designed and supervised the project. EG, CS, GC, CAS, AB contributed to data analysis. EG, GC, AB CS, CAS, MK, GC critically reviewed and provided valuable input. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest EG, GC, MK, GC, AB, CAS have none to declare; Carlo Selmi has been consulting for BMS and Pfizer.

Ethical approval The present work was approved by IRB of University of Pavia, Italy (deliberation of 12/03/2012).

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