Chronic inflammatory arthritis: patient management in the outpatient units of the italy piedmont region. Focus on cardio- and cerebro-vascular events

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Abstract

Objectives: to evaluate the cardio- and cerebrovascular events in outpatients suffering from Chronic Inflammatory Rheumatology diseases, affected by Rheumatoid Arthritis and Spondylo-Enthesitis-related Arthritis, before and after the availability of biological anti-TNFα drugs in the Piedmont region of Italy.

Methods: Data collected from a ten-year time period in three outpatient rheumatology facilities in the Piedmont region of Italy were analysed for cardio- and cerebrovascular events. In the middle of this time period, biological drugs were introduced for the outpatients.

Results: The cohort consisted of 579 rheumatology patients, of which 52.8 % were affected with Rheumatoid Arthritis and 47.2 % with spondylo-enthesitis-related arthritis. The rate of cardiovascular and cerebrovascular events was significantly lower in patients treated with biological drugs compared to those treated with synthetic anti-rheumatic drugs.

Conclusions: in this population the availability of biological anti-TNFα drugs was associated with fewer cardiovascular and cerebrovascular events in rheumatology outpatients.

Introduction

Rheumatoid Arthritis (RA) and Spondylo-Enthesitis-related Arthritis (SpA) are systemic chronic flogistic diseases which in their natural history led to progressive damage and articular deformity, with worsening of quality of life, reduced articular functionality and patients' inability to work [1-5]. In the last two decades, the therapeutic paradigm has deeply shifted. Indeed, it has been demonstrated that early treatment with synthetic Disease Modifying Antirheumatic Drugs (sDMARD), in monotherapy or combined, followed by the use of biological drugs (bDMARD) when the clinical response is inadequate, is associated with a notably better clinical and functional outcome [6-8]. Epidemiological studies have highlighted that Rheumatoid Arthritis reduces life expectancy by around 10-15 years and that cardiovascular events, above all myocardial infarction and heart failure, represent the leading cause of deaths (around half) [9-12]. Autoptic studies on Rheumatoid Arthritis patients, performed before biological drugs were available, had shown the presence of cardiovascular pathologies in around 60 % of the patients [13,14]. The prevalence of cardiovascular events in Rheumatoid Arthritis patients was similar to that observed in type II diabetes patients [15-18]. The high prevalence of cardiovascular pathology in patients affected with Chronic Arthritis is probably due to both the increase of traditional risk factors for atherosclerosis and the presence of a chronic flogistic state that induces an acceleration of the atherosclerosis process [19-21]. In physiological conditions, the vascular endothelium is involved in maintaining antithrombotic and anticoagulant homeostasis. In a flogistic state the endothelium becomes a target for cytokines, autoantibodies, and immune complexes; as a result, pro-atherogenic and pro-thrombotic modifications take place [22]. In particular, during Chronic Arthritis, the release of pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) produced in the synovial tissue seems to induce dyslipidemia, insulin resistance, and pro-atherogenic modifications in the vascular endothelium [23]. Indeed, hyperinsulinemia, insulin resistance and reduction in glucose tolerance have been observed in patients affected with Rheumatoid Arthritis, with a correlation to the severity of flogosis [24,25]. An effective drug treatment on flogosis and disease activity could be expected to reduce cardiovascular risk in patients affected with Chronic arthritis and, actually, Rheumatoid arthritis patients treated with methotrexate had shown a reduced mortality due to cardiovascular events, but not due to other causes [26].

In the last 10 years, the use of TNFα antagonist biotechnological drugs has led to a significant reduction of cardiovascular risk, despite the fact that these drugs are contraindicated in the presence of heart failure [27-31]. The treatment with TNFα antagonist biotechnological

drugs in Rheumatoid Arthritis patients has been demonstrated to significantly reduce the disease activity and the endothelium dysfunction; in addition, these drugs have shown to improve other risk factors for atherosclerosis, reducing insulin resistance (through modulation of adiponectin) and increasing High-Density Lipoprotein [32]. Moreover, in Hypertension Treatment European Guidelines, the C-reactive protein (CRP) has been included as a risk factor, predictive of cardiovascular events [33-38].

To perform a global evaluation of patients with Chronic Arthritis, taking into account the disease progression and cardio- and cerebrovascular co-morbidities, a review of ten-year clinical records was conducted in three outpatient rheumatology units in the Piedmont region of Italy.

Materials and method

Data collected from a ten-year period, on patients affected with Rheumatoid Arthritis (RA) and Spondylo-Enthesitis-related Arthritis (SpA) followed in three outpatient rheumatology facilities in Biella, Novara and Turin-1 territory, Piedmont region of Italy, were analyzed looking for lifetime cardio- and cerebrovascular events. Biological drugs were made available to these facilities in the middle of this time period. The cardiovascular events searched were cardiac (angina pectoris, acute myocardial infarction, atrial fibrillation, heart failure) and cerebrovascular (stroke, chronic vascular encephalopathy). The demographic and clinical characteristics of the population have been described, including the drug therapy taken.

Summary statistics were done, and Pearson's Chi-squared Test for Count Data or a Proportion Test were applied on the counts or proportions.

Results

Data were collected from 579 patients, with a 1.7 female/male ratio. 52.8 % of the subjects were affected with RA and 47.2 % with SpA. 47.5 % of the patients were in treatment with biological drugs (bMARD) and 52.5 % with synthetic drugs (sDMARD). Hypertension was recorded in 42.8 % of cases. Cardiovascular events were registered in 22 % of cases, 56.7 % of which were cardiac and 43.3 % cerebrovascular. In both pathologies, the female gender rate is higher, with a statistically significant difference only in the RA group (M:F = 1.3: 3.37, 70 males and 236 females) compared to the SpA group (M:F = 1:1.2, 124 males and 152 females) (Figure 1).The mean age of RA patients was 71 years, with a mean duration of disease of 17 years; the SpA patients had a lower mean age (64 years) with a mean duration of disease of 10 years.

At least one event was present in 21.9 % of patients (127 patients) of which 56.6 % were RA patients and 43.4 % SpA ones. 78 % of patients did not have any cerebro- or Events recorded: 51.7 % were RA patients and 48.3 % SpA patients.

There was a male prevalence (63 %) among SpA patients that had shown a cerebro- or cardiovascular event, and this feature was more evident in the bDMARD therapy group (p = 0.002).

The distribution of patients according to the presence of cerebro- or cardiovascular events and type of treatment was 11.1 % (bDMARD) and 88.9 % (sDMARD). In bDMARD patients, the level of events was clearly lower in both RA and SpA, with a high statistical significance (p < 0.000001) (Figure 2).

Among patients with events, 14.6 % had presented more than one, 5.5. % in therapy with sDMARD, and 0.74 % in treatment with bDMARD.
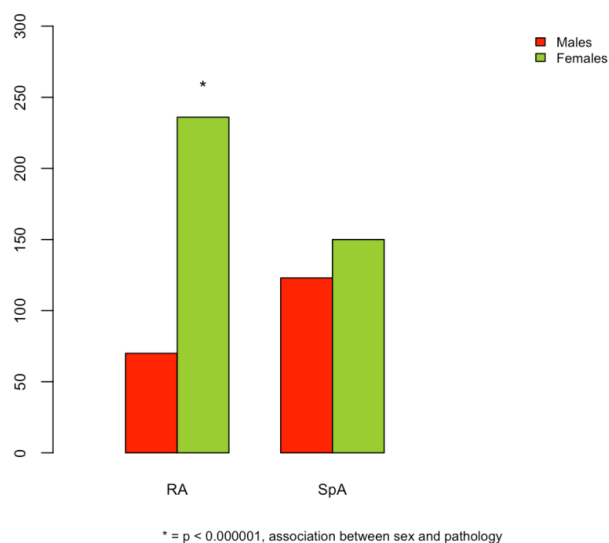

* = p < 0.000001, association between sex and pathology

Figure 1. Sex distribution according to pathology group

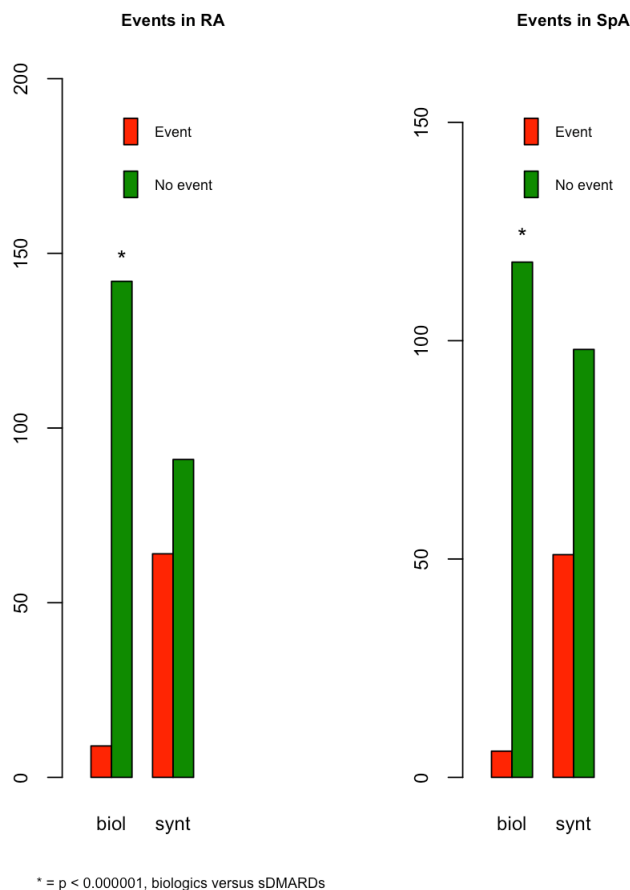* = p < 0.000001, biologics versus sDMARDs

Figure 2. Cerebro- and cardiovascular events with biological and synthetic drugs in RA and SpA patients

In the RA group, angina pectoris and acute myocardial infarction were prevalent among cardiac diseases, while multi-ischemic encephalopathy was the most frequent among cerebrovascular events. In the SpA group, the most common cardiac events were acute myocardial infarction, atrial fibrillation, and angina pectoris, while stroke was the most frequent among cerebrovascular events.

Regarding other risk factors, hypertension did not correlate with cardio- or cerebrovascular events, but there was a high percentage of missing data which could limit the interpretation of this finding.

Having a single event was the most frequent pattern (83.5 %), both with sDMARD and bDMARD.

Discussion and Conclusions

Biotechnological drugs have changed the therapeutic approach to Chronic Inflammatory Arthritis (RA and SpA), modifying the clinical progression and clearly improving patients' quality of life.

In the Piedmont region in the North of Italy, biological drugs have been available to outpatient rheumatology units since 2006. The clinical and therapeutic management of these types of patients led to a reduction in direct and indirect costs when compared to inpatient management. In addition, the continuity in the medical assistance of these chronic patients allowed the physician to have a better control of flogosis and rheumatological outcomes, as well as cerebro- and cardiovascular co-morbidities, which are the most frequent causes of death in chronic inflammatory arthritis patients. Indeed, the main objective of the work described in the present paper was to study the association between cerebro- and cardiovascular events and therapies taken by RA and SpA outpatients in three Piedmont region facilities, during a ten-year time period. This time period has allowed for the evaluation of the association between cerebro- and cardiovascular events and therapies, with possible modification of treatment during the period, starting with sDMARD and, since 2006, with bDMARD. In our population, RA patients were slightly more prevalent (52.8 %) than SpA patients (47.2 %), and more female patients were present, as expected according to scientific literature [39] (Figure 1).

Gender distribution remained globally the same, even in patients that had a cardiovascular event, but in SpA patients with cardiovascular events there were more males, and even more in biological drug treated ones (p = 0.002), as if the males were afforded less protection by biological drugs. It has to be noted that 78 % of all patients did not have any cardiovascular events and, among those with cardiovascular events, 14.2 % had the event before the diagnosis of arthritis. The secondary prevention of cardiovascular events in patients that had already had an event was more effective in patients who were treated with biological drugs (only 3 % of the total had a second event) than in patients treated with sDMARD (13 % of the total had another cardiovascular event). Our data suggests that the use of biologics could reduce cardiovascular risk.

Even with limitations due to this type of data collection, this paper can suggest the potential role of anti-TNFα drugs in reducing cardiovascular and cerebrovascular risk.

Further studies with prospective methodology, on different cohorts and of longer duration should be done to discover the actual incidence and prevalence of cardio- and cerebrovascular events during the treatment of Chronic Inflammatory Arthritis with anti-TNFα agents and/or with sDMARDs.

Acknowledgements

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