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BRIEF REPORT

Environmental Air Pollution Is a Predictor of Poor Response to Biological Drugs in Chronic Inflammatory Arthritides

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Background. There is increasing evidence that environmental air pollution is associated with the development of chronic inflammatory arthritides (CIA). The role of air pollutants on the biological treatment (biological disease-modifying antirheumatic drugs [bDMARDs]) response of CIA is still unclear.

Methods. We retrieved longitudinal data on patients affected by CIA on biological therapies and on the daily concentration of air pollutants in the Verona area. We designed a case-crossover study to compare the exposure to pollutants in the 60-day period preceding a drug switch or swap due to disease progression referent to the 60-day period preceding a visit with stable treatment for at least 6 months.

Results. A total of 1257 patients with CIA (863 with rheumatoid arthritis, 256 with psoriatic arthritis, and 138 with ankylosing spondylitis) with 5454 follow-up visits were included in the study (median follow-up 2.09 years [interquartile range: 0.82-2.58 years]). A total of 282 patients were included in the case-crossover study. We retrieved 13 636 daily air pollution records. We found that air pollutants' concentrations were higher in the 60-day period before a failure of bDMARD response and prior to a switch or swap compared with the period preceding a visit with stable bDMARD therapy for at least 6 months.

Conclusion. We found that environmental air pollution was a determinant of poor response to bDMARDs in a cohort of patients with CIA followed over a 5-year period. An intervention aimed at decreasing fossil combustion emissions might have beneficial effects on biologic persistence rates of patients with CIA and economic expenditures related to switches and swaps.

INTRODUCTION

The pathogenesis of chronic inflammatory arthritides (CIA) is complex and includes both hereditary and environmental factors (1). Air pollution, primarily produced by fossil combustion, is among the modifiable environmental factors that have been linked with the pathogenesis of CIA (2,3). This is particularly true regarding the pathogenesis of rheumatoid arthritis (RA) (4). In addition, our group has recently demonstrated that exposure to air pollution, even at low exposure thresholds, is strictly associated with RA reactivations (5). Carbon fossil combustion contains a mixture of carbon monoxide (CO), nitric oxide (NO), nitric dioxide (NO_2), oxides of nitrogen (NO_x), particulate matter with a diameter of 10 μm or 2.5 μm (PM10 and PM2.5, respectively) or less, and ozone (O_3). These substances are, in large part, shared with the toxic components contained in cigarette smoking, which has been recently recognized as the only modifiable factor associated with poor response to biological treatment (6). The evidence of such an association has not been verified for patients with psoriatic arthritis (PsA) and ankylosing spondylitis (AS); however, the biological rationale underpinning the poor response to treatment seen in patients with RA makes this association very likely in all CIA as well. Among the proposed mechanisms that can induce an aggravation of the inflammatory status in patients with CIA, there is the activation of aryl hydrocarbon receptors (7), which are predominantly expressed by Th17 cells. Furthermore, environmental air pollution has been linked to non–immune-mediated inflammatory arthritides, such as gouty arthritis, as well (8).

Northern Italy is among the most industrialized and polluted area across Europe (9), and the city of Verona, in the heart of the

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Po valley, is among the worst-ranked areas in this hapless leaderboard. Data on the quality of the air of the surroundings of Verona are collected on a daily basis by the Agenzia Regionale per la Prevenzione e Protezione Ambientale del Veneto (ARPAV), which provides detailed information on the concentrations of toxic pollutants (10).

It is of crucial importance to determine the role of air pollution on the response rate to biological disease-modifying antirheumatic drugs (bDMARDs) in order to better predict the response to therapies of CIA. Such information can help translate basic research finding into clinical evidence to inform health policy makers more precisely. The primary objective of the present study is to determine the association between the concentration of air pollutants and biological drug retention rates in CIA.

PATIENTS AND METHODS

We extracted clinical data on patients with CIA from the registry of biological therapies of the University of Verona. We collected longitudinal data of patients affected by CIA starting from September 2013 to September 2018. The following characteristics were available: ZIP code of residency, demographic characteristics, treatment with antirheumatic medications (including all available bDMARDs for CIA at the time of evaluation, nonsteroidal antiinflammatory drugs, corticosteroids, methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine), the presence of comorbidities, C-reactive protein (CRP) serum levels, and disease activity score assessed with Disease Activity Score 28–CRP (DAS28-CRP) for RA and PsA and AS Disease Activity Score (ASDAS) for AS.

Data on the daily concentration of air pollutants in the Verona area from June 2013 to September 2018 were collected. The following air pollutants were available: concentration (mg/m^3) of CO, concentration (μg/m^3) of NO, concentration (μg/m^3) of NO_2, concentration (μg/m^3) of NO_x, concentration (μg/m^3) of PM10, concentration (μg/m^3) of O_3, and concentration (μg/m^3) of PM2.5. We included in the study only patients with residency (determined by ZIP code) in the Verona area (ie, within 10 km from the air pollutant collection). Five air quality stations were available for data collection in the Verona's area. The location of the stations is available at http://geomap.arpa.veneto.it/maps/106/view. Patients were linked to the respective air quality station's data.

To determine the association between air pollutant concentrations and biological drug switch or swap we designed a case-crossover analysis. The case-crossover analysis is described extensively in our previously published paper (5). In brief, we analyzed the concentration of air pollutants (CO, NO, NO_2, NO_x, PM10, O_3, and PM2.5) as area under the curve (AUC) and mean concentration during the 60-day period before every appointment with the rheumatologist. We compared the exposure to pollutants before the switch or swap visit with the exposure before a visit with stable biological treatment for at least 6 months. We enrolled patients with at least two consecutive visits available and with at least one switch or swap of biological treatment. If more than one visit fulfilled the prespecified criteria (ie, more than one visit with switch or swap and more than one visit with stable treatment for at least 6 months), the average concentration exposure among visits was considered. In this scheme, every patient contributed to a hazard period (the 60 days preceding the switch or swap) and a control period (the 60 days preceding the stable treatment visit). The two appointments were separated by a period of at least 3 months. We excluded from the analyses all bDMARD failures due to adverse events of drug intolerance. We conducted sensitivity analyses by analyzing the exposures as geometric means and cumulative concentrations and by considering the 30-day period of exposure. Data on air pollutants were collected from the official, open-source bulletin of the ARPAV (available on request).

Discriminatory capacity for the prediction of switch or swap due to drug inefficacy was assessed with the receiver operating characteristic (ROC) curve, which was based on binary logistic regression models (with switch as binary dependent variable). Model 1 included disease activity, Model 2 included air pollution exposure, and Model 3 included both disease activity and air pollution exposure. For this purpose, in Model 2 and Model 3, all air pollutants were included in the regression model (mean 60 days exposure prior to switch/no switch).

Group comparisons were performed with Student's *t* tests and Mann-Whitney U tests (for normally and non-normally distributed continuous variables, respectively). All differences were considered significant when the *P* value was less than 0.05. All statistical analyses were performed using SPSS version 26 (SPSS, Inc).

The study was conducted according to the protocol BIOREVE (BIOlogici REgione VEneto) 534CESC and approved by our local ethics committee in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

Data on 1257 patients affected by CIA (863 patients with RA, 254 with PsA, and 138 with AS) with 5454 follow-up visits and 13636 daily air pollution records from June 2013 to September 2018 were retrieved. Table 1 shows the descriptive characteristics of the cohort stratified by disease. With regard to RA, we found 370 bDMARD switches or swaps (10.9% of the total amount of visits) due to inefficacy of the treatment and 2750 visits with stable biological therapy (81.0% of the total amount of visits). Regarding PsA, we found 188 drug switches or swaps (14.3%) and 1006 visits with stable biological therapy (76.7%). Concerning AS, we found 82 drug switches or swaps (11.0%) and 590 visits with stable biological therapy (79.1%). Mean disease activity (DAS28-CRP for RA and PsA and ASDAS for AS) and CRP levels were higher at the switch or swap visits as compared with stable treatment visits (Table 1). Considering the overall cohort (5454 visits) we found

Table 1. Characteristics of the study population

Variable	Patients With RA (n = 863; 3396 Follow-Up Visits)	Patients With PsA (n = 256; 1312 Follow-Up Visits)	Patients With AS (n = 138; 746 Follow-Up Visits)
Female sex, n (%)	681 (78.9)	118 (45.2)	49 (35.8)
Height, mean ± SD, cm	166.8 ± 8.9	169.8 ± 8.9	170.5 ± 9.2
Weight, mean ± SD, kg	71.3 ± 14.9	76.3 ± 14.8	74.4 ± 15.0
Disease duration, mean ± SD, years	12.1 ± 9.6	7.1 ± 6.1	8.2 ± 7.3
Seropositive, n (%)	529 (61.3)	0 (0)	0 (0)
DAS28-CRP (ASDAS for AS), mean ± SD	2.71 ± 0.83	2.39 ± 1.26	1.80 ± 1.17
DAS28-CRP (ASDAS for AS) at visit with stable biological treatment, mean ± SD	2.40 ± 1.01	2.15 ± 1.07	1.62 ± 1.03
DAS28-CRP (ASDAS for AS) at visit with drug switch or swap, mean ± SD	4.27 ± 1.10[a]	3.78 ± 1.25[a]	3.23 ± 1.31[a]
CRP, median (IQR), mg/L	4.71 (0.5-7.1)	2.00 (1.0-4.0)	2.00 (1.0-5.0)
CRP at visit with stable biological treatment, median (IQR), mg/L	2.00 (1.0-5.0)	1.60 (1.0-3.0)	2.00 (1.0-4.0)
CRP at visit with drug switch or swap median (IQR), mg/L	5.00 (2.0-12.0)[b]	4.40 (2.0-8.9)[b]	5.00 (2.0-10.0)[b]
bDMARDs (first prescribed), n (%)			
Abatacept	119 (13.8)	2 (0.8)	0 (0)
Adalimumab	171 (19.8)	63 (24.6)	43 (31.5)
Certolizumab	60 (6.9)	15 (5.9)	7 (4.8)
Etanercept	221 (25.6)	53 (20.7)	15 (10.9)
Golimumab	110 (12.9)	31 (12.1)	31 (22.2)
Infliximab	76 (8.8)	10 (3.9)	14 (10.4)
Rituximab	21 (2.4)	0 (0)	0 (0)
Secukinumab	0 (0)	71 (27.7)	28 (20.2)
Tocilizumab	85 (9.8)	0 (0)	0 (0)
Ustekinumab	0 (0)	11 (4.3)	0 (0)
csDMARDs, n (%)			
Methotrexate	365 (42.3)	75 (29.2)	13 (9.5)
Leflunomide	147 (17.0)	26 (10.0)	2 (1.0)
Hydroxychloroquine	47 (5.5)	1 (0.1)	0 (0)
Glucocorticoids			
Taking, n (%)	571 (66.2)	118 (46.1)	37 (26.8)
Dose, median (IQR), mg prednisone eq	1.42 (0.0-4.3)	0.0 (0.0-5.0)	0.0 (0.0-0.0)

Abbreviation: AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; bDMARD, biological disease-modifying antirheumatic drug; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS-CRP, Disease Activity Score 28–C-reactive protein; IQR, interquartile range; PsA, psoriatic arthritis; RA, rheumatoid arthritis.
[a] $P < 0.001$ compared with disease activity at visit with stable treatment.
[b] $P < 0.001$ compared with CRP at visit with stable treatment.

that patients with elevated CRP levels (≥5 mg/L) were exposed to higher levels of air pollutants concentrations (AUC 60-day period before assessment). We found an exposure-dependent relationship between exposure to air pollutants and CRP serum levels in CIA. At PM10 exposures of more than 50 µg/m^3 and 40 µg/m^3, we found a 150% and 65% higher risk of having CRP levels of more than 5 mg/L (odds ratio [OR] 2.564; 95% confidence interval [CI] 2.114-3.110 and OR 1.659; 95% CI 1.440-1.910, respectively). If the threshold was set at 30 µg/m^3 PM10 (below the European Union health protection limit), we still found a 38% higher risk of having altered CRP levels (OR 1.383; 95% CI 1.206-1.588).

Among patients with CIA, 280 patients (22.3%) had at least two follow-up visits with at least one bDMARD switch or swap due to drug inefficacy and at least one visit with stable treatment for at least 6 months, serving as our sample for the case-crossover study. We found that air pollutant concentrations were higher before a switch or swap due to drug inefficacy. Figure 1 shows the mean concentrations of air pollutants in the 60-day period before switch or swap visits compared with the stable treatment visits. Sensitivity analysis (geometric mean, cumulative concentrations, and considering the 30-day period of exposure) yielded similar results (data not shown).

Figure 2 shows the ROC curve for the prediction of switch or swap due to drug inefficacy. Discriminatory capacity of disease activity alone was the highest (AUC = 0.841), but when the prediction model included the concentrations of air pollutants in the 60 days before the visit, the discriminatory capacity increased (AUC = 0.879).

DISCUSSION

We conducted a retrospective analysis on a cohort of more than 1000 patients affected by CIA followed over a period of 5 years. Overall air pollution was associated with systemic inflammation as assessed by CRP serum levels. Exposure to air pollutants was higher before treatment failures and treatment switches

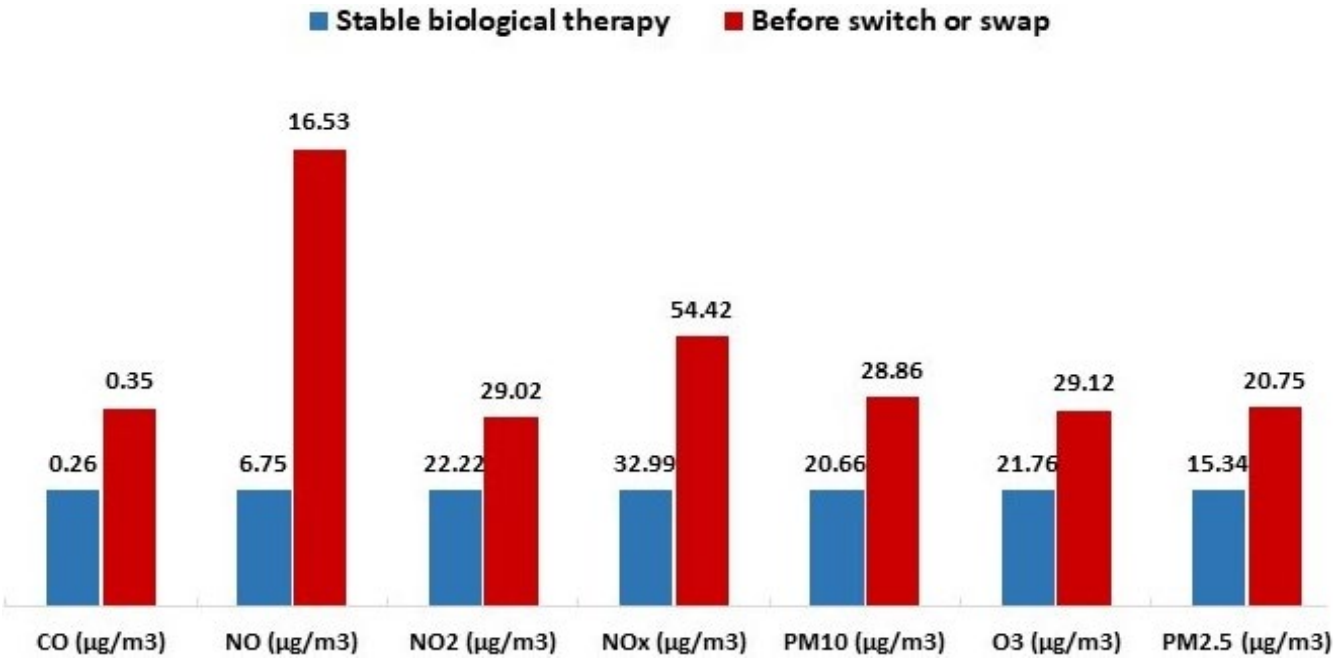

Figure 1. Mean concentrations of air pollutants in the 60-day period before switch or swap visits compared with the stable treatment visits. *P* < 0.001 within groups. PM2.5, particulate matter with a diameter of 2.5 µm; PM10, particulate matter with a diameter of 10 µm.

or swaps due to drug inefficacy compared with the exposure before visits with stable bDMARD treatment for at least 6 months.

Toxic air pollutants have been previously linked with an increased risk of developing RA (3,4), but just a few studies have explored the association between environmental air pollution and disease activity of RA (5,11). In addition, our group has recently proved that air pollution is strictly related to reactivations of the disease and CRP serum levels in patients with RA (5). All this evidence provided a solid rationale for the present analysis. Interestingly, we found that, among the pollutants in study, differences

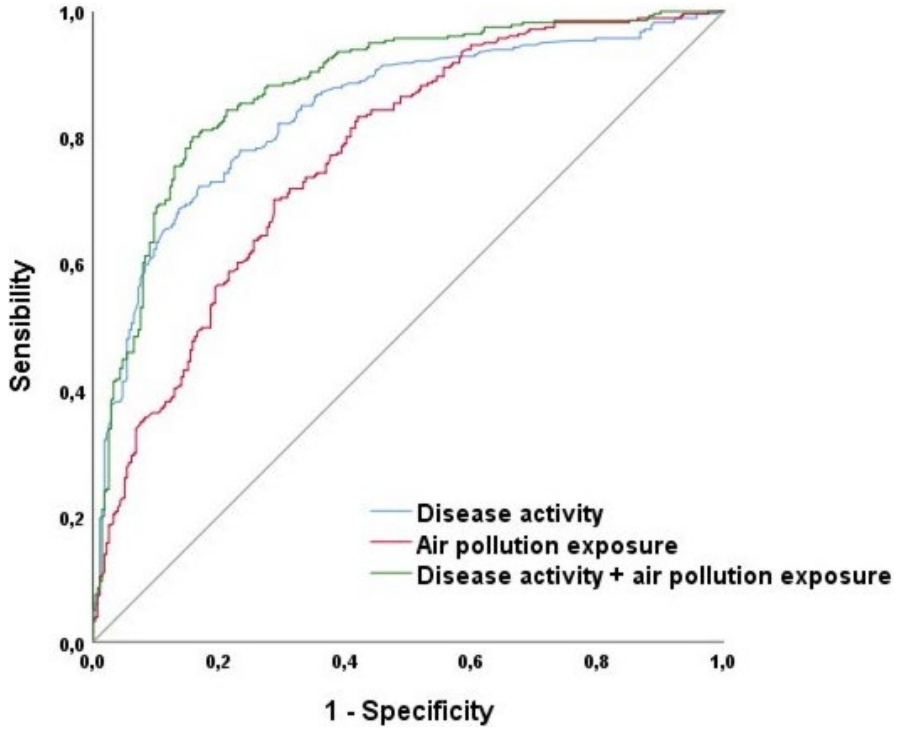

Figure 2. Receiving operating characteristics curves for the prediction of switch or swap due to drug inefficacy.

in NO concentrations between switch or swap visits and stable treatment visits were more conspicuous compared with those seen in other pollutants (Figure 1). This finding is in line with preclinical studies (12,13) and has a highly plausible rationale. Indeed, NO, which has been found elevated in synovial tissue of patients with arthritis (12), plays a central role in the pathogenesis of autoimmune inflammatory arthritides (13). Therefore, is not surprising that traffic-derived NO was markedly elevated before bDMARD switches or swaps.

The present analysis focused on the risk of poor response to bDMARDs in patients with CIA. We found that approximately 10% of the patients of the cohort switched or swapped biological drugs over a median follow-up period of 2.09 years (interquartile range: 0.82-2.58 years), which approximately equates to 5% of patients switching every year. As expected, we found that most of the drug switches can be explained by disease activity alone (AUC of the ROC curve = 0.841); however, when we added to the prediction model the exposure to air pollutants in the 60-day period before the assessment, the AUC increased to 0.879, which translated to a slightly improved prediction ability. Indeed, approximately 4.5% of the drug switches or swaps owing to bDMARD inefficacy can be explained by air pollution alone. Notably, we excluded from the analyses all the treatment failures related to adverse events or intolerance, which might have been affected by air pollution. In our analysis, disease activity was only partially reflective of treatment switch. This finding means that there are other unmeasured factors that might determine treatment switches, and such factors were probably mediated, at least in part, by air pollution exposure. Therefore, we can hypothesize, for example, that some components of disease activity were more strongly associated with drug switches than others and that the same factors might have a stronger link with air pollution than others.

To estimate the economic burden of air pollution on CIA, we can adopt a scenario of switching from an anti-Tumor Necrosis Factor biosimilar with an average annual cost per patient ranging from $5000 to $20 000 to a bDMARD with another mechanism of action with an annual cost per patient ranging from $15 000 to $60 000. In this setting, if we imagine an optimistic reduction of carbon fossil emissions by a half, we might avoid approximately 2.25 of 100 bDMARD switches or swaps, with roughly $22 500 to $90 000 saved every year (assuming a cohort of 2000 patients with a 5% switch rate every year, which translates into 100 bDMARD changes per year). Nonetheless, there is no way of predicting whether a treatment switch will be from a less expensive to a more expensive bDMARD. Therefore, the most important implication of the present study is clinical.

Our study has strengths and limitations. Key strengths of our study are the longitudinal and case-crossover designation and the large sample size. In addition, we had access to a wide range of air pollutants with daily measurement in a highly polluted region (the Po Valley). Nevertheless, we should acknowledge some limitations related to the data source. Indeed, we did not have access to pulmonary or cardiovascular comorbidities and to the smoking status that might have affected drug switches or swaps. In addition, even if we have excluded from the analyses all the switches and swaps due to drug intolerance or adverse events, some drug intolerances or adverse events might have been erroneously labeled as drug inefficacies. Nevertheless, it is unlikely that misclassifications were common enough to alter our findings. We conducted the case-crossover study by pooling together all CIA with possible exchangeability problems. Nevertheless, stratification is fundamental to attain exchangeability in cohort and case-control studies; in contrast, patients in case-crossover studies are assumed to be conditionally exchangeable given the nature of the study, in which each subject serves as case and control at the same time. In addition, our study should be interpreted in view of limitations common to all ecological studies. For example, the use of average exposure levels may have masked more complicated relationships between CIA and air pollution. Moreover, exposure data were available at the area level, with possible misclassification because of nonregistered relocations. In addition, we did not have access to data regarding weather conditions or outdoor temperature, which might be determinants of both drug switch and air pollution concentrations. Indeed, weather conditions (eg, rain) can reduce the concentration of air pollutants; this is a well-known phenomenon called “wet deposition,” and it is reasonable to think that weather conditions and temperature might affect disease activity of patients with CIA. However, only some of the components of air pollution precipitate during rainy days; for example, larger particulate matter is drastically reduced by rain, whereas smaller pollutants or gaseous pollutants are not meaningfully affected by weather conditions at all (14).

To our knowledge, this is the first study demonstrating a possible relationship between environmental air pollution exposure and poor response to biological therapies in CIA. In order to ascertain such an association, we designed a case-crossover study that controls for between-patient and within-person time-invariant confounding, and we have demonstrated that air pollution is associated with a higher risk of bDMARD switches or swaps. In our cohort of patients with CIA, approximately 5 of 100 biological drug switches or swaps were probably attributable to the sole effect of air pollution.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Giovanni Adami and Prof. Maurizio Rossini had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Giovanni Adami; Data curation

Acquisition of data. Giovanni Adami and Maurizio Rossini.

Analysis and interpretation of data. Giovanni Adami, Maurizio Rossini, Ombretta Viapiana,Giovanni Orsolini, Eugenia Bertoldo, Marco Pontalti,Camilla Benini, Elena Fracassi, Alessandro Giollo,Davide Gatti and Angelo Fassio.

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