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Polypharmacy in Early Rheumatoid Arthritis: Impact on Treatment Response and Adverse Event Risk in a multicenter French prospective cohort study

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Objective. The objective of this study was to assess whether polypharmacy (PP) was associated with treatment response and serious adverse events (SAEs) in early rheumatoid arthritis (RA). Additionally, we aimed to investigate whether PP could serve as a surrogate marker for comorbidities.

Methods. We used data from the French cohort ESPOIR, a prospective study of early RA. PP was defined as a categorical variable stratified into two or three categories according to median of distribution in the cohort. A logistic regression model was used. We assessed the occurrence of SAEs (severe infections, hospitalizations, deaths) throughout a 10-year follow-up period.

Results. The proportion of patients who achieved DAS 28 remission (REM) one year after the initiation of the first disease-modifying antirheumatic drug (DMARD) was 32.1% in the PP group versus 67.9% in the non-PP group (P = 0.07) from 497 patients included. At five years, the proportion with REM was 45.0% in the PP group versus 56.3% in the non-PP group (P = 0.03). Patients taking two or more medications (excluding RA therapy) had a 40% lower likelihood of achieving REM at five years (adjusted odds ratio [OR] 0.60 [95% confidence interval (CI) 0.38–0.94], P = 0.03). At 10 years, patients receiving multiple medications had a 43% lower probability of achieving REM (adjusted OR 0.57 [95% CI 0.34–0.94], P = 0.02). The incidence of SAEs was 61 per 1,000 person-years. Among patients who developed SAEs, 86.4% were in the PP group and 49.8% were in the non-PP group (P = 0.03).

Conclusion. PP is associated with a poorer treatment response and increased risk of SAEs. PP may serve as a good surrogate marker of comorbidities in epidemiologic studies.

INTRODUCTION

Polypharmacy (PP) is a public health concern especially in developed countries. Defined as "the administration of many drugs simultaneously or by the administration of an excessive number of drugs" for an individual, there is no consensus on the medication threshold defining PP.[1,2] It is worth noting that PP has doubled in the last 15 years.[3] In the United Kingdom, patients taking more than five drugs rose from 11% to 21%, and PP's prevalence is steadily increasing.[3] The upward trend in PP can be attributed first to the aging of the population, which contributes to a higher prevalence of comorbidities. Secondly, the advancement in medical treatments have led to the development of increasingly specialized drugs. Rheumatoid arthritis (RA) management has been improved over the last 20 years, and clinical guidelines recommend the use of conventional synthetic disease-modifying antirheumatic drugs (DMARDs) alone or in combination with targeted DMARDs (biologic DMARDs or targeted synthetic DMARDs). Their

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combination with the usual treatments of patients (comorbidities, analgesics) contributes to multiple prescriptions.

Despite significant advancements in the management of RA, the burden of morbidity associated with the condition remains high.[4] This can largely be attributed to the presence of comorbidities (such as infections, cancers, cardiovascular diseases, and osteoporosis) that impact both the quality of life and the prognosis of individuals with RA, as well as their response to treatment.[5,6] Comorbidities pose a challenge in research studies because they act as confounding factors; however, there is currently no consensus on the standardized measurement of comorbidities.[5,7] Comorbidity indices are currently used to estimate the weight of comorbidities in a patient. These indices are a composite outcome, which adds specific diseases (that may or may not be weighted) as a single number. They are influenced by the collection of often declarative data and may not accurately reflect the polypathology.[8,9] They might provide only a limited ability to control for confounding factors.[10]

The number of medications and the presence of PP are easier to obtain because treatments are often carefully collected in studies. Furthermore, they may reflect active comorbidities, whereas comorbidity indices include past or current pathologies. In RA, a study of 1,001 patients showed that PP (taking more than 10 drugs vs less than 5) increased the risk of hospitalization (hazard ratio [HR] 3.1 [95% confidence interval (CI) 2.1–4.5]).[11] Moreover, PP is also associated with serious adverse events (SAEs) (HR 1.13 [95% CI 1.12–1.13]), including drug-related problems (odds ratio [OR] 2.9 [95% CI 1.5–5.9]).[12,13]

Bechman et al[13] reported from the BSRBR-RA cohort study that PP can reduce treatment response. For each additional drug added, the likelihood of achieving a favorable EULAR response at one year after starting a biologic DMARD decreased by 8% (OR 0.92 [95% CI 0.91–0.93]).[13] The impact of PP on treatment response in RA remains poorly understood.

The primary objective of this study was to investigate the association between PP and treatment response at 1, 5, and 10 years after initiation of the first DMARD in patients with early RA. Our secondary objective was to assess the impact of PP on the occurrence of SAEs during a 10-year follow-up period. Furthermore, we aimed to explore the association between PP and comorbidity indices within a population of individuals with early RA in France.

MATERIALS AND METHODS

Study data. We used data from the French ESPOIR cohort study (the study and follow-up of early undifferentiated arthritis), a multicenter early-onset arthritis cohort study.[14] With the participation of 14 investigating centers, 813 patients aged 18 to 70 years with at least two swollen joints developing for 6 weeks to 6 months, were included between November 2002 and April 2005. Clinical, laboratory, and imaging data were collected at baseline, then every 6 months for the first 2 years, and then once a year for at least 10 years. Data were collected by a regional university rheumatology center that did not interfere with the patient's therapeutic management. The protocol of the ESPOIR cohort study was approved by the Ethics Committee of Montpellier, France (July 2002; no. 020307). All patients gave their signed informed consent.

Eligibility criteria. All patients included in the ESPOIR cohort were recruited for a 5- and 10-year follow-up. Among the whole population, we selected patients meeting the 2010 American College of Rheumatology (ACR) criteria for diagnosis of RA during the first year of follow-up and starting their first DMARD within 24 months of inclusion in the cohort.[22] Our population of patients respond to the definition of early RA developing for six months. For the primary objective, the selected population met the previous criteria and were required to have available activity data (Disease Activity Score in 28 joints using the erythrocyte sedimentation rate [DAS28-ESR]) at the evaluation date (ie, 1, 5, and 10 years after starting the first DMARD). The 10-year follow-up initial population (RA diagnosis, starting their first DMARD within 24months) was studied for the occurrence of SAEs.

Baseline assessment. Baseline data collected included demographics, RA characteristics, DAS28-ESR, Health Assessment Questionnaire (HAQ) score, smoking status, DMARDs, glucocorticoids, analgesics, other medications, and comorbidity. Comorbidity burden was scored using the Rheumatic Disease Comorbidity Index (RDCI), which contains 11 comorbidities, and the modified RDCI (mRDCI), which adds two other conditions (body mass index [BMI] and chronic kidney failure). We chose to use the RDCI comorbidity score because it is an index developed specifically for patients with chronic inflammatory rheumatism to predict physical disability as well as death.[15,16]

Follow-up. Disease activity data were collected at 1, 5, and 10 years after initiation of the first DMARD. Comorbidities and medication count were collected at baseline (for 1-year treatment response analysis) and 5 years (for 5-, 10-year treatment response analysis and SAE evaluation). Medications were collected at each visit by an investigator and verified by a study nurse. The ESPOIR cohort database was closed in 2015 for the 10-year follow-up because all patients reached the 10-year follow-up between December 2012 and June 2015.

PP definition. Medication count included all specialties excluding background RA therapy, such as analgesics and nonsteroidal anti-inflammatory drugs, glucocorticoids, topicals, homeopathic treatments, vitamin therapies, venotonics, anti-infectious treatments taken on an ad hoc basis, and phytotherapy. PP was defined as a categorical variable stratified into two or three categories according to median (0–1 and ≥2) or tertiles

(0 [ref], 1–2, and ≥3) of distribution in the ESPOIR cohort. The median and sometimes the tertiles were used because the total number of medications was low (young patients, hence relatively low PP).

Outcomes definition. Treatment response was assessed by achieving DAS28-ESR remission (REM) at 1 year, 5 years, and 10 years after initiation of the first DMARD. The occurrence of SAEs was measured by the occurrence of severe infection (required intravenous drug or caused death), hospitalization (more than one day), or death during the 10-year follow-up.

Statistical analysis. Baseline characteristics of the study population were presented using mean ± SD for quantitative variables and frequency (percentage) for categorical variables. Univariable analysis was conducted to examine the relationship between patient characteristics and the achievement of REM, as well as the occurrence of SAEs. The chi-square test was used for qualitative variables, whereas covariance analysis was employed for quantitative variables. Logistic regression analysis was performed to assess the associations between PP and REM at 1, 5, and 10 years (primary outcome). We adjusted for age, sex, BMI, duration of disease, initial DAS28-ESR, baseline HAQ score, smoking status, RDCI, and mRDCI for multivariable analysis. For SAEs, we calculated the occurrence of SAEs by 1,000 person-years (PY). Each event was treated in a binary manner (occurrence or nonoccurrence), and then we conducted multivariable analysis. We used baseline PP to evaluate the achievement of REM in the one-year treatment response analysis. For the 5- and 10-year treatment response analyses, as well as the analysis of the occurrence of SAEs, we considered the presence of PP at 5 years. To account for comorbidities, we incorporated the RDCI and mRDCI at baseline for the one-year treatment response analysis. For the analysis of treatment response at 5 and 10 years and the occurrence of SAEs, we used the corresponding RDCI and mRDCI indices measured at the 5-year mark. This approach allowed us to capture the impact of comorbidities on treatment outcomes and SAE occurrence throughout the study duration. By using baseline and five-year indices of the RDCI and mRDCI, we aimed to reflect the evolving nature of comorbid conditions and their potential influence on the assessed outcomes over time.

We conducted several multivariable models to explore the relationships between the variables of interest. In the first model, we adjusted for all potentially associated variables ($P < 0.2$). In the second model, we excluded the RDCI and mRDCI to examine the specific contribution explained by PP alone. Additionally, we investigated the impact of each added drug by considering the number of drugs in the analysis. Pearson correlation was conducted to look for an association between PP and comorbidity indices. $P < 0.05$ was considered statistically significant. SPSS was used for statistical analysis.

RESULTS

Baseline characteristics. From 813 patients registered in the ESPOIR cohort, 543 met the 2010 ACR/EULAR criteria and started a DMARD during the first year of follow-up;[22] 497 patients had disease activity data and were included for the 1-year treatment evaluation (382 at 5 years and 323 at 10 years) (Figure A S1 in Supplementary Files). The baseline characteristics are listed in Table 1 and Table A in the Supplementary Files). The mean age was 48.6 years, the mean ± SD baseline DAS28 was 5.4 ± 1.20, and 77.2% of patients were female

Medication, PP, and comorbidities. Cardiovascular (27%), metabolic and endocrine (21%), and digestive (20%) drug classes were most commonly used. The mean ± SD number of drugs excluding RA therapy at baseline was 1.5 ± 1.70 (median 1, first tertile 0, second tertile between 1 and 2, third tertile ≥3 [all

Table 1. Baseline characteristics of patients and follow-up*

	Baseline (n = 543)	5-y follow-up (n = 382)
Age, mean ± SD, y	48.6 ± 11.9	–
Female, n (%)	419 (77.2)	–
BMI, mean ± SD	25.1 ± 4.6	–
Tobacco exposure (current and/or past), n (%)	258 (47.5)	–
RF and/or ACPA positive, n (%)	372 (68.5)	–
RA duration, mean ± SD, days	103.4 ± 53.8	–
Radiographic erosions, n (%)	138 (25.4)	–
C-reactive protein, mean ± SD, mg/L	23.8 ± 35.2	–
HAQ, mean ± SD	1.0 ± 0.7	–
DAS28-ESR, mean ± SD	5.4 ± 1.20	–
RDCI score, mean ± SD	1.2 ± 0.9	1.1 ± 1.1
mRDCI score, mean ± SD	1.4 ± 1.2	1.5 ± 1.5
Number of non-RA medications, mean ± SD	1.5 ± 1.7	1.9 ± 2.15
Cumulative csDMARDs, mean ± SD	NA	1.5 ± 0.8
Cumulative bDMARDs, mean ± SD	NA	0.4 ± 0.7
NSAID, mean ± SD	0.75 ± 0.44	NR
Analgesics, mean ± SD	0.66 ± 0.58	NR
10-y cumulative glucocorticoids, mean ± SD, mg/day	2.78 ± 0.74	–

*ACPA, anticitrullinated protein antibodies; bDMARD, biologic DMARD; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-ESR, Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; mRDCI, modified RDCI; NA, not applicable; NR,not reported; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; RDCI, Rheumatic Disease Comorbidity Index; RF, rheumatoid factor.

Table 2. Association between PP and DAS28 remission at 1, 5, and 10 y after initiation of the first DMARD*

	Non-PP[a] group, %	PP[a] group, %	Univariable analysis, *P*	Multivariable analysis[b]	
				OR (95% CI)	*P*
First year: DAS28 remission (n = 190/497)	67.9	32.1	0.07	0.97 (0.64–1.48)	0.90
5 y: DAS28 remission (n = 196/382)	**56.3**	**45.0**	**0.03**	**0.60 (0.38–0.94)**	**0.03**
10 y: DAS28 remission (n = 83/305)	67.5	32.5	0.06	**0.57 (0.34–0.94)**	**0.02**

*Bold values indicate statistical significance. BMI, body mass index; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; OR, odds ratio; PP, polypharmacy.
[a]PP according to the median.
[b]Adjusted for age, sex, baseline DAS28 and HAQ scores, disease duration, smoking status, BMI, and erythrocyte sedimentation rate; Rheumatic Disease Comorbidity Index and modified Rheumatic Disease Comorbidity Index were excluded.

ranged from 0 to 9]). The mean ± SD number of drugs at the five-year follow-up was 1.94 ± 2.15 (median 1, first tertile 0–1, second tertile 2, and third tertile ≥3 [all ranged from 0 to 13]) (Table 1). When PP was defined by the median, 36.7% of patients were polymedicated at baseline and 44.2% were polymedicated at five years. The most common comorbidities were cardiovascular diseases (36.1% at baseline, 65.4% at five-year follow-up), depression (62.1% at baseline, 41.4% at five-year follow-up), and endocrinal diseases (30.2% at baseline, 36.1% at five-year follow-up) (Table B and Figure B in Supplementary Files). At baseline, the mean ± SD RDCI score was 1.2 ± 0.9 and the mean ± SD mRDCI score was 1.4 ± 1.2 (Table 1).

PP and treatment response. One year after initiation of the first DMARD, the proportion of patients in REM was significantly lower in the PP group: 39.5% in REM for the first tertile, 43.7% in REM for the second tertile, and 16.8% in REM for the third tertile (*P* = 0.03; Table 2). If PP was defined by the median, the proportion of patients who achieved REM was 32.1% in the PP group versus 67.9% in the non-PP group (*P* = 0.07). There was no association between PP and treatment response at one year in multivariable analysis. At five years, the proportion of patients in REM was 45.0% in the PP group versus 56.3% in the non-PP group (*P* = 0.03). The DAS28 was higher as the tertile of drug distribution (Figure 1). If comorbidity indices were not included in multivariable analysis, patients who took two or more medications had a 40% lower probability of achieving REM (OR 0.60 [95% CI 0.38–0.94], *P* = 0.03) at five years from the first DMARD. The addition of each medication decreased the probability of achieving REM by 14% (OR 0.86 [95% CI 0.77–0.96], *P* = 0.007). At 10 years, patients receiving multiple medications had a 43% lower probability of achieving REM (OR 0.57 [95% CI 0.34–0.94], *P* = 0.02).

PP and SAEs. After 10 years of follow-up, the incidence of all-cause SAEs was 61 per 1,000 PY, and 86.4% of patients with all-cause SAEs were in the PP group versus 49.8% in the non-PP group (*P* = 0.03; Table 3). Baseline and five-year number of drugs was higher in the SAEs group (mean ± SD 1.61 ± 1.77 vs 1.31 ± 1.54, *P* = 0.045; and mean ± SD 2.17 ± 2.24 vs 1.55 ± 1.92, *P* = 0.003, respectively). Comorbidities and glucocorticoids were associated with SAE occurrence (OR 1.57 [95% CI 1.26–1.96],

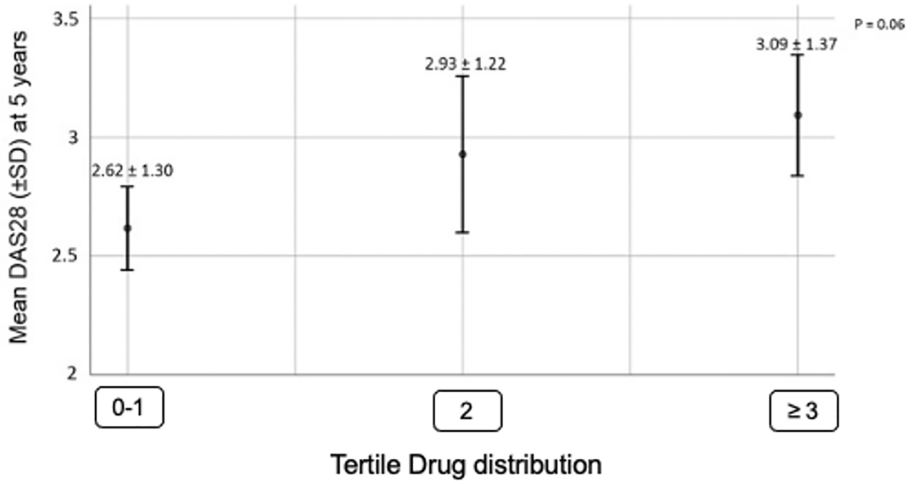

Figure 1. DAS28 at five years according to PP expressed in tertiles (0–1 [ref], 2, ≥3). DAS28, Disease Activity Score in 28 joints; PP, polypharmacy.

Table 3. Occurrence of SAEs during 10-y follow-up by PP status*

	Non-PP group (0–1), % (n/N)	PP group (≥2), % (n/N)	*P*
Serious infections (n = 41)	5.6 (16/285)	15.4 (25/162)	0.02
Hospitalization (n = 272)	48.4 (138/285)	82.7 (134/162)	0.004
Death (n = 18)	2.4 (7/285)	6.8 (11/162)	0.13
All-cause SAEs (n = 285)	49.8 (145/285)	86.4 (140/162)	0.03

*PP, polypharmacy; SAE, serious adverse event.

$P < 0.001$; and OR 1.24 [95% CI 1.11–1.38], $P < 0.001$). Hospitalization was the most frequent SAE (58 per 1,000 PY), and the proportion was higher in the PP group (82.7% vs 48.4%; $P = 0.004$). Similar results were found with serious infections, which occurred in 9.1 per 1,000 PY, with a higher proportion in the PP group (15.4% vs 5.6%; $P = 0.02$). Few deaths occurred during follow-up (n = 18 [4.0%]), and no significant difference was found between the groups. All these results were no longer significant in multivariable analysis.

PP as a surrogate marker of comorbidities. In the PP group (according to the median or tertile), comorbidity indices were higher, and we found a linear relationship between the number of drugs and comorbidity scores ($P < 0.001$) (same findings at baseline and five-year evaluation; Figure 2, Table C in Supplementary Files). There was a moderate association between the number of drugs and the RDCI (r = 0.47, $P < 0.01$) and mRDCI (r = 0.49, $P < 0.01$) scores at baseline. To provide further insight into variables for adjustment, a directed acyclic graph was drawn (Figure 3).

DISCUSSION

Our study shows an association between PP and RA disease activity at 1, 5, and 10 years after initiation of a first DMARD in patients with early RA. Disease activity increases linearly with non-RA medications in patients with early RA. The occurrence of SAEs was associated with PP.

PP complicates the management of RA and may contribute to higher disease activity in these patients.[17–19] Our data are consistent with the literature. Filkova et al[11] found a higher mean DAS28 at baseline in patients taking more than 10 drugs versus less than 5 (mean ± SD DAS28 4.24 ± 1.38 vs 3.33 ± 1.60; $P < 0.001$). Gomides et al[18] also found higher DAS28 scores in patients with multiple medications, but as in our study, these results were not confirmed in multivariable analysis. As in our study, Bechman et al[13] focused their analysis on response to treatment. They found that the proportion of patients achieving a good EULAR response (defined as having DAS28 scores of 3.2 or less with reductions in DAS28 scores of more than 1.2) decreased by 22% in patients taking more than 10 drugs compared with patients taking less than 5 (OR 0.78 [95% CI 0.65–0.92], $P < 0.01$) after adjustment for age, sex, and RDCI score. As in our study, when Bechman et al[13] adjusted for confounders (age, sex, smoking status, DAS28 and HAQ scores at inclusion, BMI, duration of disease progression, RDCI score), the association was no longer significant.

During the 10-year follow-up, we found that patients with PP had a higher number of SAEs. In the BSRBR-RA cohort, the

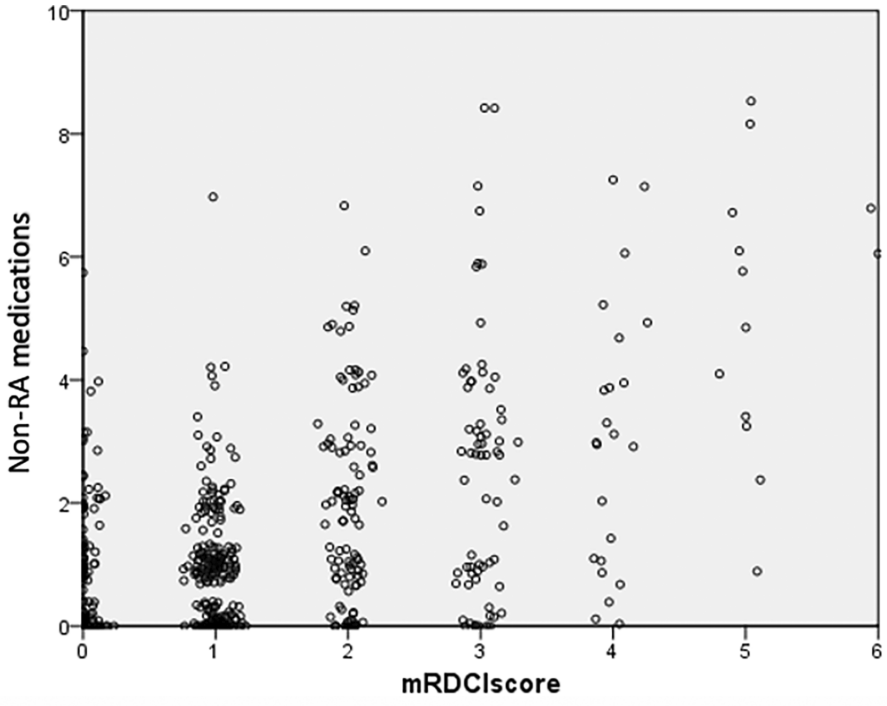

Figure 2. Plot of the mean difference of comorbidity indices and number of non-RA medications (at baseline). mRDCI, modified Rheumatic Disease Comorbidity Index; RA, rheumatoid arthritis.

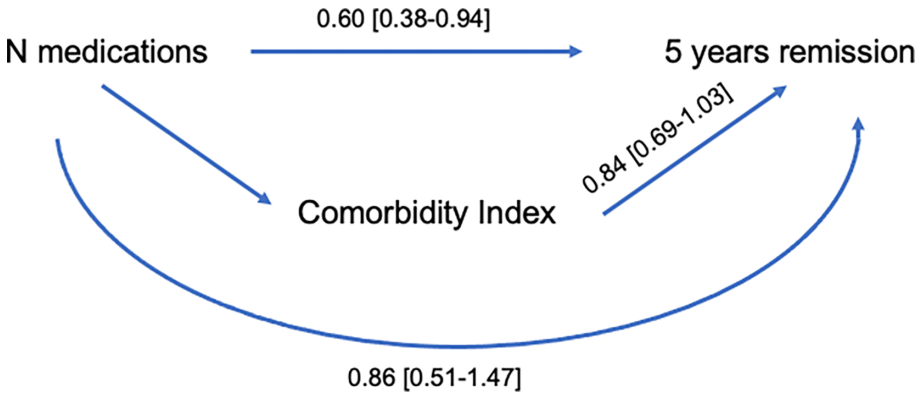

Figure 3. Five-year analysis directed acyclic graph.

authors found a 49% excess risk of SAEs in patients taking more than 10 drugs versus less than 5 (HR 1.49 [95% CI 1.38–1.61], $P < 0.01$).[13] Using data issued from the same cohort, Subesinghe et al[20] showed that PP was a risk factor for recurrent infections (OR 1.26 [95% CI 1.13–1.41]). For patients with PP up to 10 drugs, this risk was the highest (OR 1.74 [95% CI 1.47–2.07]). Concerning the risk of hospitalization, Filkova et al[11] showed that taking more than 10 drugs versus less than 5 multiplied the number of hospitalizations by three (HR 3.1 [95%CI 2.1–4.5]). After adjustment for confounding factors, including comorbidity indices, our study did not show an association between PP and treatment response or SAEs occurrence.

Regarding the limitations of our study, the assessment of treatment response at one year after the initiation of the first DMARD could be a limitation because the medications changes in the meantime were not taken into account. Similarly, using PP collected at 5 years for 10-year treatment response and for SAE assessment could not reflect the medications change; accordingly, comorbidity burden reflected by PP could be less reliable. Other limitations are missing data, retrospective collection of serious infections, and the inability to assess medication adherence or verify actual medication use. The ESPOIR cohort is a French multicenter cohort representative of France, but its generalization to other countries with different sociocultural or socioeconomic contexts cannot be ensured. The strengths of our study are the prospective design, multicentric setting, and large sample (n = 543) from the French cohort ESPOIR, with standardized data collection completed by experienced investigators.

We found an association between the number of non-RA medications and comorbidity indices. Based on the findings of this study, we propose that PP could serve as a useful surrogate for comorbidity indices, offering a more straightforward and easily collectible tool. Given that the number of non-RA medications is correlated with both comorbidity burden and the frequency of adverse events, several interrelated mechanisms may underlie this relationship. It should also be noted that comorbidities influence the poorer treatment response (depression at baseline reduces the likelihood of a good therapeutic response and decreases long-term improvement).[21] Pharmacological interactions may reduce the efficacy of certain DMARDs. The restricted use of specific DMARDs in the context of comorbidities (eg, methotrexate in patients with chronic pulmonary diseases) further complicates treatment strategies. Finally, some comorbidities may be reflected by PP, whereas others are not (eg, smoking).

Future considerations regarding PP in patients with RA should involve a thorough analysis of patient prescriptions and the evaluation of potential drug–drug interactions by clinical pharmacists. Medication reconciliation is already being integrated in certain hospital settings to address this challenge. The potential for prescription optimization through regular review and simplification could be an interesting avenue for further research.

To conclude, PP is associated with increased disease activity, poorer treatment response, and an increased risk of SAEs. The results are no longer significant after adjustment for comorbidity indices, and further studies are needed. However, it highlights the tight link between PP and comorbidity burden and supports PP as a valuable, valid comorbidity tool.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation

AND drafting or reviewing/editing the final draft. As corresponding author, Dr Benamar confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSORS

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