


ORIGINAL RESEARCH

Suboptimal management of rheumatoid arthritis in France: a real-world study based on data from the French National Health Data System

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ABSTRACT

Objectives The emergence of targeted therapy is changing rheumatoid arthritis (RA) management, but real-world data remain limited. This study aimed to describe real-world RA treatment patterns using data from a French national claims database.

Methods This longitudinal study used the French Permanent Representative Sample (Echantillon Généraliste des Bénéficiaires) claims database. Patients with RA were identified between 2013 and 2017, with treatment patterns, persistence and adherence described.

Results The study population included 2553 patients with RA. Disease-modifying antirheumatic drugs (DMARDs) were prescribed for 1512 (59.2%) patients, of whom 721 (47.6%) did not require discontinuation or treatment switch. There were 377 (24.9%) treatment discontinuations and 114 patients (7.5%) switched to a targeted DMARD (biological and synthetic (Janus kinase inhibitor) DMARDs). Among the 2315 patients with RA in 2017, almost half (n=1102, 47.6%) were not treated with a DMARD. Most (85.7%) received symptomatic treatment (analgesics (81.0%), steroids (49.2%), non-steroidal anti-inflammatory drugs (39.5%)). Of the 1142 treatment initiations identified, 713 (62.4%) were conventional synthetic DMARDs (csDMARDs), with methotrexate being the most frequent (n=553, 48.45%). One-year persistence rates varied between 55.9% (49.2–62.0%) for tumour necrosis factor inhibitors, and 63.4% (59.6–67.0%) for csDMARDs. Treatment adherence, assessed through medication possession ratio, varied between 71.9% and 90.8%, with ≥80% being the adherence cut-off. Almost half of DMARD initiations were associated with long-term (>6 months), high-dose oral steroid use (~7 mg/day prednisone equivalent).

Conclusion Despite a diverse therapeutic arsenal, there remains a medical need that is not covered by current RA management, which is frequently compensated for by overprescription of steroids.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease, characterised by dense lymphocytic infiltration into the

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rheumatoid arthritis (RA) is a major public health concern in France, affecting about 200 000 patients. Methotrexate is the ‘gold-standard’ treatment for RA, as part of a treat-to-target principle, and can be associated with other disease-modifying antirheumatic drugs (DMARDs), notably biologics. However, little is known about real-life management of RA in France, particularly current treatment patterns and need for biological DMARDs and corticosteroids.

WHAT THIS STUDY ADDS

⇒ This study showed RA prevalence was underestimated, with more than 300 000 patients estimated currently. It also confirmed methotrexate as a cornerstone in RA management, being used to treat almost 66% of patients; a need for targeted DMARDs was noted in 15% of patients, notably biologics as a second-line therapy. Despite the treat-to-target principle, almost half of patients did not receive any DMARD. Also, long-term corticosteroid therapy (>6 months) remains widespread, although guidelines recommend this as an acute therapy. Finally, 10% of patients stop their treatment early, probably because of non-response, intolerance or non-compliance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Despite the large variety of therapies available, the management of patients with RA remains suboptimal, and an unmet medical need seems to persist—especially among untreated patients (who are still very numerous), but also among non-responders and intolerant/non-compliant patients.

synovial cavity. Reduced functional capacity and increasing difficulty in performing professional activities worsen patients’ quality of life.¹ Worldwide, RA prevalence ranges from 0.3% to 1.3%.^{2–4} According to recent French data, RA prevalence has increased in recent years, with 200 000 patients reported in

2017,⁵ partly as a result of the greater numbers of elderly patients with increasing life expectancy.⁶

RA management is multidisciplinary and should begin immediately following diagnosis, with treatment initiation, psychological support, regular physical activity, diet management and coordinated follow-up in order to reach remission.⁷ Treatment includes conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and targeted DMARDs (tDMARDs), which include both biological (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). Methotrexate is considered the 'gold standard' for RA management and must be initiated as monotherapy immediately upon diagnosis, when not contraindicated.^{8,9} The progressive implementation of clinical and biological objectives for treatment adaptation associated with a closer follow-up (treat-to-target principle) has led to significant improvements in RA management.¹⁰

Several studies describing the epidemiology and management of RA based on claims databases have been published, notably in Europe and in the USA. These studies provide robust algorithms which enable the identification of RA in medicoadministrative databases, and emphasise the importance of DMARDs, notably methotrexate, in the management of RA.^{11–16} For instance, more than 55% of patients with RA from the UK receive long-term (>1 year) DMARD treatment, and more than 60% of German patients initiate RA treatment with methotrexate.^{11,12}

However, real-world data on RA treatment patterns in France remain limited and French prevalence assessments, via long-duration disease (LDD), seem inaccurate. The most recent real-world studies of RA management in France do not use data beyond 2015 and are largely focused on describing the drug therapies used rather than treatment patterns.^{13,17–19} The aims of this study were: (1) to present updated data on RA epidemiology in France; (2) to describe the main RA treatment patterns, from initiation of a systemic therapy (DMARD) to therapeutic escalations, encompassing treatments used, treatment persistence and co-prescriptions in line with guidelines; and (3) to describe the main characteristics and symptomatic drug use among patients not treated with DMARDs. Real-world data from the Echantillon Généraliste des Bénéficiaires (EGB) French representative sample were used.

METHODS

Study design

This was a non-interventional, retrospective, longitudinal, descriptive study of treatment sequences and patterns in a cohort of patients with RA, identified in the EGB. Patients were selected from 1 January 2013 to 31 December 2017 and were followed from index date, defined as the date of first RA-related event occurring during selection period, or 1 January 2013 if an RA-related event occurred before, to 31 December 2017 or death, whichever occurred first.

Data source

Data from the French National Healthcare Database (Système National des Données de Santé (SNDS)) include claims data covering 99% of the total French population. EGB is a 1/97th random sample from the SNDS and is representative of the French population in terms of age and sex.

Study population

Patients were included in the population with RA if they: (1) had continuous enrolment in a health insurance scheme between 2010 and 2017; (2) had at least one RA-related event during 2010–2017; and (3) were aged ≥ 18 years at index date. RA-related events included LDD for RA, based on codes from the International Classification of Diseases–10th revision (ICD-10) M05 and M06, and hospitalisation with ICD-10 codes M05 (and subcodes M05.x) and M06 (and subcodes M06.x except M06.1–*adult-onset Still disease*) as the main, related or associated diagnosis.

Patients with hospitalisation or LDD for lupus erythematosus, scleroderma or myositis were excluded. After a medical review considering other indications with potential arthritic repercussions (arthritis, ankylosing spondylitis and other systemic inflammatory diseases), patients with LDD or hospitalised for ankylosing spondylitis who did not present an LDD for RA were also excluded. Detailed algorithms are available in the online supplemental file.

The RA cohort was split between treated patients (receiving a DMARD during follow-up, including already-treated patients) and untreated patients (without any DMARD during follow-up). Within the treated population with RA, patients with RA treatment initiation within the selection period were identified.

Outcomes and statistical analyses

General methods

Quantitative variables were described as mean (SD) or median (Q1, Q3). Qualitative variables were described as absolute number and percentage (95% CI (CI₉₅)). Analyses were performed using SAS V.9.4 (SAS Institute).

Patient characteristics

Within the treated population with RA, sociodemographic characteristics were described at index date. Medical and treatment history and comorbidities were assessed over a 3-year period prior to index date. Charlson Comorbidity Index (CCI) was described at index date based on a validated SNDS algorithm.²⁰ Patient characteristics were described in untreated patients. Results were extrapolated (CI₉₅) for 2017, adjusted for sex and age.²¹ The proportion of untreated patients with RA receiving symptomatic RA treatment (non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids or pain medication) 1 year after index date was estimated. Algorithms for the identification of medical history and comorbidities are available in the online supplemental file.

Treatment modalities

Treatment modalities were assessed using two approaches, namely treatment sequences and treatment initiations. The first approach aimed to describe the potential treatment escalation for a patient during follow-up, taking the first course of treatments encountered at inclusion (monotherapy or combination) as the starting point, for both newly treated and previously treated patients. The second approach aimed to describe treatment use at the time of initiation, specifically in relation to their combination with other DMARDs or corticosteroids, irrespective of the patients per se. A figure describing the study design and the methodology for the assessment of treatment-related outcomes is available in the online supplemental figure 1.

RA treatment sequences

Treatment sequences correspond to the succession of treatments, associations, switches and discontinuations for the same patient during follow-up. The most frequent RA treatment sequences (>1% of patients) were described in the treated population with RA. Treatments of interest were methotrexate, other csDMARDs and tDMARDs, alone or in combination. tDMARDs included bDMARDs with tumour necrosis factor inhibitors (TNFis), anti-interleukin therapy, T cell modulators or anti-lymphocyte B cell therapy, and tsDMARDs with Janus kinase inhibitors (JAKis). Discontinuation status was defined as a period of ≥ 3 months (12 months for rituximab) without any dispensation after the period covered by the last observed treatment.

RA treatment initiations

Treatment initiations were described for each DMARD initiated between 2013 and 2017 until discontinuation and/or end of follow-up, without considering the patient concerned. Initiation of a DMARD was considered if no dispensation of said DMARD was observed within 3 years before initiation. The number and proportion of treatment initiations, as monotherapy or combination therapy, were evaluated. Treatment association was defined as an overlap of at least the coverage period of a treatment, plus 1 week. Early treatment discontinuation was defined as treatment discontinuation with ≤ 2 dispensations within 2 months after initiation, with no further dispensation. The proportion of RA treatment initiations in combination with long-term oral corticosteroids (≥ 6 months) was assessed.

Persistence and adherence

Persistence and adherence to RA treatments were described in patients initiating RA treatment between 2013 and 2017 until discontinuation and/or end of follow-up. Treatment duration (CI_{95}) was described by Kaplan-Meier analysis. DMARD persistence rates were also described. Treatment adherence was estimated by calculating the medication possession ratio (MPR). Good adherence was defined as an MPR of $\geq 80\%$.²²

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Identification of population with RA

Of the 738 185 patients identified from the EGB between 1 January 2013 and 31 December 2017, 2760 reported an RA-related event, of whom 2748 were aged ≥ 18 years at index date (figure 1). Patients with lupus erythematosus (n=55), scleroderma (n=21), myositis (n=12) and ankylosing spondylitis without active LDD for RA (n=119) were excluded. The population with RA included 2553 patients, including 1512 (59.2%) treated and 1041 (40.8%) untreated patients. A total of 1142 treatment initiations were recorded in 794 patients. In 2017 (n=2314), the extrapolated French population with RA was 307 612 (CI_{95} : 306 530 to 308 698).

Description of study population

The characteristics of population with RA are described in table 1. Mean age (SD) was 64.4 (15.8) years; 73.4% of patients were female. Only 4.9% of patients had free-of-charge health coverage (Couverture Médicale Universelle complémentaire). In total, 12.7% of patients had a medical history of interest; 9.9% had a history of solid cancer. One-third (34.0%) of patients with RA reported comorbidities, including pulmonary diseases (17.4%), diabetes (13.2%) and chronic heart failure (10.9%). Approximately one-third of patients with RA had a CCI score of ≥ 5 , one-third had a score of 3 or 4, and one-third had a score of ≤ 2 . At least one reimbursement for RA treatment within 3 years prior to index date was recorded for 81.6% of patients; 72.5% received an oral corticosteroid, 44.8% received a DMARD, 41.6% of which received a csDMARD, 1% received a modulator of T cell co-stimulation and 0.6% received other immunosuppressive treatments.

RA treatment sequences

The most frequent RA treatment sequences in the treated population with RA (n=1512) are described in table 2. Methotrexate was the most frequent treatment, accounting for 64.7% of the most frequent sequences (>1% of sequences) identified. In total, 47.7% (n=721) of patients received a single treatment without discontinuation or switch, of which 35.0% (n=529) received methotrexate, 3.4% (n=51) received another csDMARD and 9.3% (n=141) received a tDMARD. In 9.5% of patients (n=144), a treatment switch to a tDMARD was recorded. Treatment discontinuation was reported for 25% of patients (n=377), of which 20.2% (n=305) were initially receiving methotrexate, 3.0% (n=46) tDMARDs and 1.7% (n=26) csDMARDs.

RA treatment initiations

Details of treatment initiations during follow-up are described in table 3. A total of 1142 RA treatment

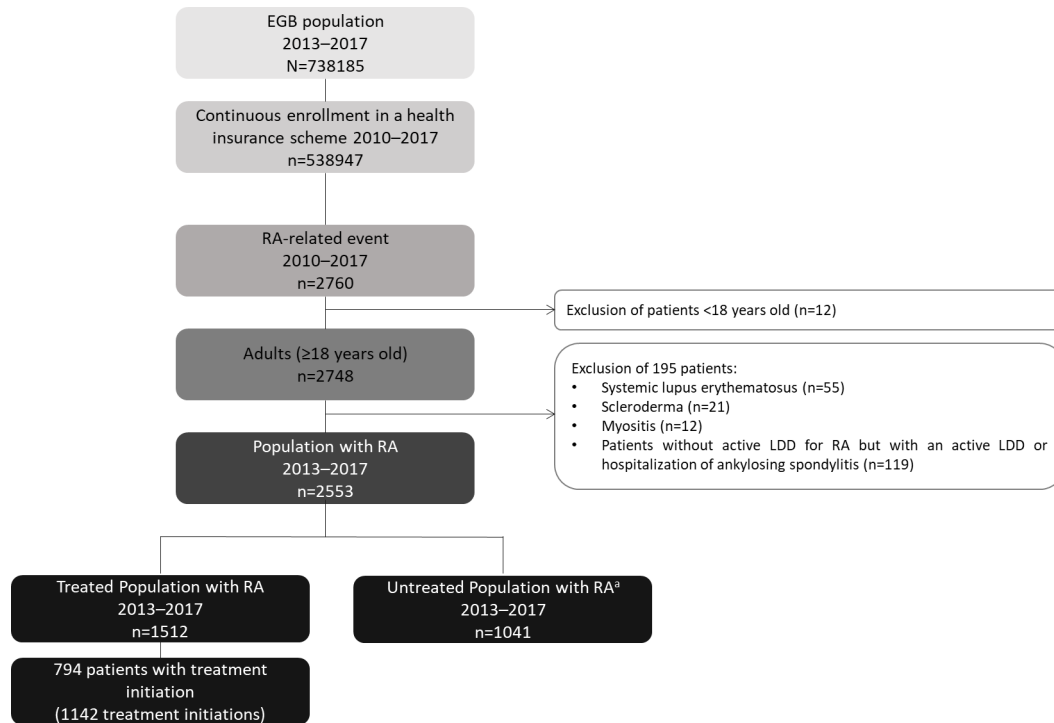


Figure 1 Selection of the study population with RA in EGB. ^aPatients without any DMARD treatment from the index date to 31 December 2017 or death, whichever came first. DMARD, disease-modifying antirheumatic drug; EGB, Echantillon Généraliste des Bénéficiaires; LDD, long-duration disease; RA, rheumatoid arthritis.

initiations were identified during the study period, in 794 patients. Initiation of csDMARDs was reported in 62.4% (n=713) of treatment initiations, 82.5% (n=588) of which were monotherapies. Methotrexate was the most commonly initiated csDMARD (48.4%, n=553). TNFi accounted for 22.1% (n=252) of all initiations, 34.9% (n=88) of which were monotherapies. Other tDMARDs represented 15.5% (n=177) of treatment initiations, 33.9% (n=60) of which were monotherapies.

The proportion of early treatment discontinuations ranged from 3.4% for certolizumab pegol to 46.6% for sulfasalazine. Discontinuation rates were 15.5%, 10.7% and 11.9% for csDMARDs, TNFis and other tDMARDs, respectively. The early discontinuation rate for methotrexate was ~10%.

Among the 713 csDMARD initiations, 252 TNFi initiations and 177 tDMARD initiations, 42.6% (n=304), 39.7% (n=100) and 53.1% (n=94) were associated with long-term oral corticosteroids, respectively. Median (Q1, Q3) duration of the association between long-term oral corticosteroids and csDMARDs, TNFi treatment or other tDMARDs was 12 months (6.7, 22.0), 9.1 months (5.9, 18.6) and 8.9 months (5.2, 16.6), respectively. Average (SD) oral corticosteroids dose, in mean daily prednisone equivalents, ranged from 7.8 (4.9) mg for other tDMARDs to 6.5 (4.1) mg for TNFis.

Persistence and adherence to RA treatments

Following RA treatment initiation, the 12-month persistence rates (CI₉₅) for csDMARDs, TNFis and other tDMARDs were 63.4% (59.6% to 67.0%),

55.9% (49.2% to 62.0%) and 59.4% (51.2% to 66.6%), respectively. At 24 months, they were 52.4% (48.3% to 56.4%), 45.5% (38.6% to 52.1%) and 39.8% (31.4% to 48.1%), respectively. Median treatment duration ranged from 3.4 to 38.7 months for csDMARDs, 11.4 to 41.5 months for TNFis and 13.0 to 22.1 months for other tDMARDs (figure 2). Mean MPR for csDMARDs, TNFis and other tDMARDs were 80.5%, 90.8% and 71.9%, respectively. Mean MPR was 79.9% for methotrexate (figure 3).

Untreated population with RA

Over the entire study period, 1041 (40.8%) patients with RA did not have any dispensation of DMARDs. These patients had a mean (SD) age of 70.5 (15.8) years and 26.4% were male. The mean (SD) CCI score was 5.0 (2.8), and 55.3% of patients had a CCI score ≥5 (table 1). In the 3 years prior to index date, 95.7% (n=996) of patients received at least one treatment for symptoms of RA (oral corticosteroids, NSAIDs or pain medication); 65.3% (n=680) received oral corticosteroids, 67.6% (n=704) NSAIDs and 92.5% (n=963) pain medications. Only 13.4% (n=140) of untreated patients received a DMARD in the 3 years prior to index date, of which 13.0% (n=135) were csDMARDs. Within 1 year of the index date, 87.3% (n=909) of patients received symptomatic treatments: 81.0% (n=843) received pain medication, 49.2% (n=512) oral corticosteroids and 39.5% (n=411) NSAIDs.

Table 1 Characteristics of the overall and untreated population with RA (N=2553)

| Characteristics | Overall population with RA (N=2553) | Untreated population (N=1041) |
|---|-------------------------------------|-------------------------------|
| Female, n (%) | 1873 (73.4) | 766 (73.6) |
| Age (years), mean (SD) | 64.4 (15.8) | 70.5 (15.8) |
| Age (years), n (%) | | |
| <40 | 168 (6.6) | 46 (4.4) |
| 40–50 | 301 (11.8) | 75 (7.2) |
| 50–60 | 479 (18.8) | 123 (11.8) |
| 60–70 | 582 (22.8) | 175 (16.8) |
| 70–80 | 498 (19.5) | 235 (22.6) |
| ≥80 | 525 (20.6) | 387 (37.2) |
| CMU-c beneficiaries, n (%) | 125 (4.9) | 53 (5.1) |
| LDD beneficiaries, n (%) | 2001 (78.4) | 825 (79.3) |
| Duration of disease at index date among patients with RA and LDD (years), n (%) | | |
| 0–5 | 874 (43.7) | 333 (32.0) |
| 5–10 | 410 (20.5) | 307 (29.5) |
| 10–15 | 305 (15.2) | 166 (15.9) |
| ≥15 | 412 (20.6) | 235 (22.6) |
| Medical history, n (%) | | |
| Patients with at least one medical history of interest | 323 (12.7) | – |
| Solid cancer | 252 (9.9) | – |
| Myocardial infarction | 38 (1.5) | – |
| Tuberculosis | 29 (1.1) | – |
| Lymphoma | 15 (0.6) | – |
| Herpes zoster with hospitalisation | 6 (0.2) | – |
| Comorbidities, n (%) | | |
| Patients with at least one chronic comorbidity of interest | 867 (34.0) | – |
| Pulmonary diseases (interstitial lung disease and/or bronchiectasis and/or chronic obstructive pulmonary disease and/or asthma) | 443 (17.4) | – |
| Chronic heart failure | 279 (10.9) | – |
| Diabetes | 336 (13.2) | – |
| Neurological diseases (demyelinating diseases) | 8 (0.3) | – |
| CCI score, n (%) | | |
| 0 | 52 (2.0) | 0 (0.0) |
| 1–2 | 754 (29.5) | 195 (18.7) |
| 3–4 | 822 (32.2) | 271 (26.0) |
| 5–6 | 570 (22.3) | 317 (30.5) |
| ≥6 | 355 (13.9) | 258 (24.8) |
| Treatment history*, n (%) | | |
| At least one reimbursement of RA treatment | 2083 (81.6) | 714 (68.6) |
| Oral corticosteroid therapy† | 1850 (72.5) | 680 (65.3) |
| DMARD | 1144 (44.8) | 140 (13.4) |
| csDMARD‡ | 1062 (41.6) | 135 (13.0) |
| TNFi§ | 264 (10.3) | 15 (1.4) |
| Modulator of T cell co-stimulation¶ | 26 (1.0) | <11 (<1.1) |
| Other immunosuppressive treatments of interest** | 16 (0.6) | <11 (<1.1) |

*Within 3 years of the index date.
 †Including betamethasone, dexamethasone, methylprednisolone, prednisolone, prednisone and hydrocortisone.
 ‡Including methotrexate, sulfasalazine and leflunomide.
 §Including adalimumab, certolizumab pegol, etanercept, golimumab and infliximab.
 ¶Including abatacept, anti-interleukin 6, tocilizumab, sarilumab, JAKi, baricitinib, tofacitinib, anti-interleukin 1, anakinra, anti-lymphocyte B and rituximab.
 **Including azathioprine.
 CCI, Charlson Comorbidity Index; CMU-c, Couverture Médicale Universelle complémentaire; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; JAKi, Janus kinase inhibitor; LDD, long-duration disease; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

Table 2 Most frequent RA treatment sequences among the treated population with RA (n=1512)

| Treatment sequences | n (%) |
|--|------------|
| Methotrexate (without discontinuation) | 529 (35.0) |
| Methotrexate–treatment discontinuation | 171 (11.3) |
| Methotrexate–targeted DMARD | 144 (9.5) |
| Targeted DMARD (without discontinuation) | 141 (9.3) |
| Methotrexate–treatment discontinuation–methotrexate | 84 (5.6) |
| Other csDMARDs (without discontinuation) | 51 (3.4) |
| Methotrexate–treatment discontinuation–methotrexate–treatment discontinuation | 34 (2.3) |
| Targeted DMARD–treatment discontinuation | 27 (1.8) |
| Other csDMARDs–treatment discontinuation | 26 (1.7) |
| Targeted DMARD–treatment discontinuation–targeted DMARD | 19 (1.3) |
| Methotrexate–treatment discontinuation–methotrexate–treatment discontinuation–methotrexate | 16 (1.1) |

Patients receiving a DMARD between the index date and 31 December 2017 or death, whichever occurred first.

Other csDMARDs correspond to non-methotrexate csDMARDs (ie, sulfasalazine and leflunomide).

csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis.

Table 3 Treatment initiations by DMARD (n=1142)

| Treatment | Treatment initiation, n (%) | Treatment initiated as monotherapy, n (%) |
|-----------------------|-----------------------------|---|
| csDMARD | 713 (62.4) | 588 (82.5) |
| Methotrexate | 553 (48.4) | 465 (84.1) |
| Leflunomide | 85 (7.4) | 72 (84.7) |
| Sulfasalazine | 73 (6.4) | 49 (67.1) |
| Hydroxychloroquine | 0 (0.0) | – |
| Chloroquine | 2 (0.2) | – |
| TNFi | 252 (22.1) | 88 (34.9) |
| Adalimumab | 67 (5.9) | 28 (41.8) |
| Certolizumab pegol | 29 (2.5) | 8 (27.6) |
| Etanercept | 96 (8.4) | 29 (30.2) |
| Golimumab | 37 (3.2) | 15 (40.5) |
| Infliximab | 23 (2.0) | 8 (34.8) |
| Other targeted DMARDs | 177 (15.5) | 60 (33.9) |
| Abatacept | 71 (6.2) | 23 (32.4) |
| Tocilizumab | 53 (4.6) | 15 (28.3) |
| Sarilumab | 0 (0.0) | – |
| Baricitinib | 3 (0.3) | – |
| Tofacitinib | 0 (0.0) | – |
| Anakinra | 9 (0.8) | – |
| Rituximab | 41 (3.6) | 18 (43.9) |

Patients receiving a DMARD between the index date and 31 December 2017 or death, whichever occurred first.

Proportion of treatment initiated as monotherapy corresponds to the ratio of monotherapies divided by treatment initiations for the same treatment (eg, for csDMARD: 588/713=82.5%).

csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor.

DISCUSSION

This study showed that, in 2017, more than 300 000 (307 602) patients with RA were living in France, of whom 83% (n=255 318) had an LDD for RA (217 600 according to the French National Health Insurance). This highlights the limitation of LDD for disease detection in French claims databases and the need for validated algorithms. The extrapolated prevalence was around 0.46%, in line with the recent study by Pina Vegas and the French EPIHARE group (0.47%).²³ Studies in Europe showed similar results with 0.4–0.5% in Germany, 0.7% in England and 0.77% in Sweden, potentially highlighting a North–South geographical gradient.^{24–26}

DMARD therapeutic strategy and corticosteroid use

As expected based on the current guidelines, this study highlights that methotrexate remains the cornerstone of RA therapy, representing more than 60% of the treatment sequences identified. The treatment sequences do not consider the potential treatments received before the study period, implying that patients identified with another treatment (other csDMARDs, tDMARD) might have previously received methotrexate. The treatment sequences also emphasise the treat-to-target principle; 35.0% of patients received methotrexate as monotherapy, reflecting potential dose escalations or switches to the subcutaneous form; a therapeutic escalation to tDMARD, occurred in at least 9.5% of patients.^{7 8 27} Similar results were reported in Germany by Gossen *et al*, with 61.8% of patients initiating RA treatment with methotrexate. On the other hand, sulfasalazine, hydroxychloroquine and leflunomide were only received by around 5% of patients in our study. The study by Gossen *et al* reported more than 10% of patients receiving these treatments, highlighting different treatment practices between countries, despite common guidelines.¹¹

Treatment initiations were in line with the guidelines, with csDMARDs, notably methotrexate, largely initiated as monotherapy. tDMARDs were frequently associated with another treatment (commonly methotrexate) at initiation. Among patients with an inadequate response or intolerance to methotrexate and an absence of adverse prognostic factors, the main treatment options are methotrexate optimisation via dose escalation or switching to subcutaneous forms, or a switch to/combination with another csDMARD. tDMARDs should be considered if this strategy fails or is contraindicated, as they are intended to be initiated in association with csDMARDs.^{7 8 28 29} Furthermore, a history of intolerance or contraindication to methotrexate is the main reason for tDMARD monotherapy, with intolerance rates estimated between 10% and 40% in several smaller-scale studies.^{30–32}

In contrast to the long-term management of RA, which is based on DMARDs, the treatment of flares is symptomatic and primarily relies on corticosteroids and NSAIDs. In addition to their use during acute episodes,

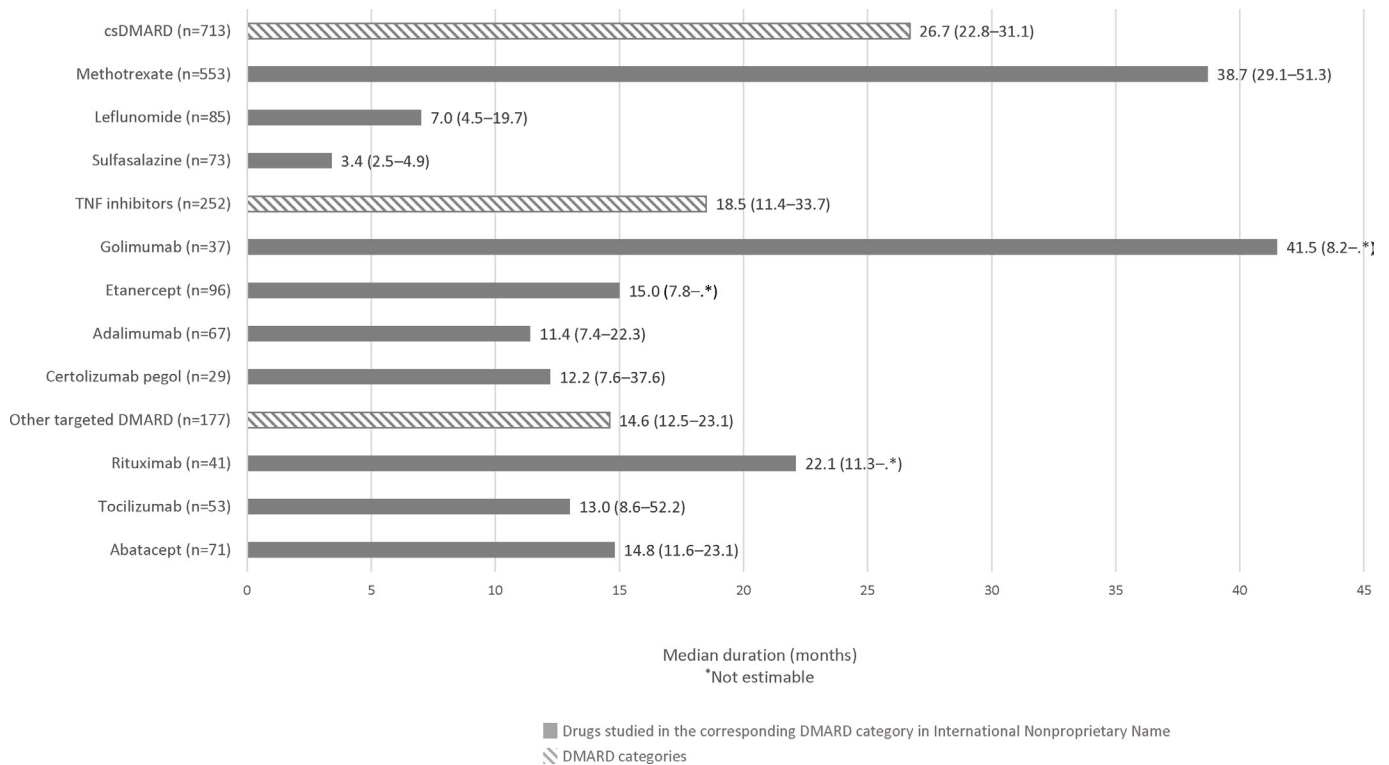


Figure 2 Median duration of RA treatments in months (CI_{95%}) (n=1142 RA treatment initiations). csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

and according to the 2014 and 2018 French Society of Rheumatology recommendations, oral corticosteroids can be used to cover potential delays between the

initiation of a DMARD and its clinical effects. In these circumstances, corticosteroids can be initiated in parallel to the DMARD, at the lowest dose and duration possible

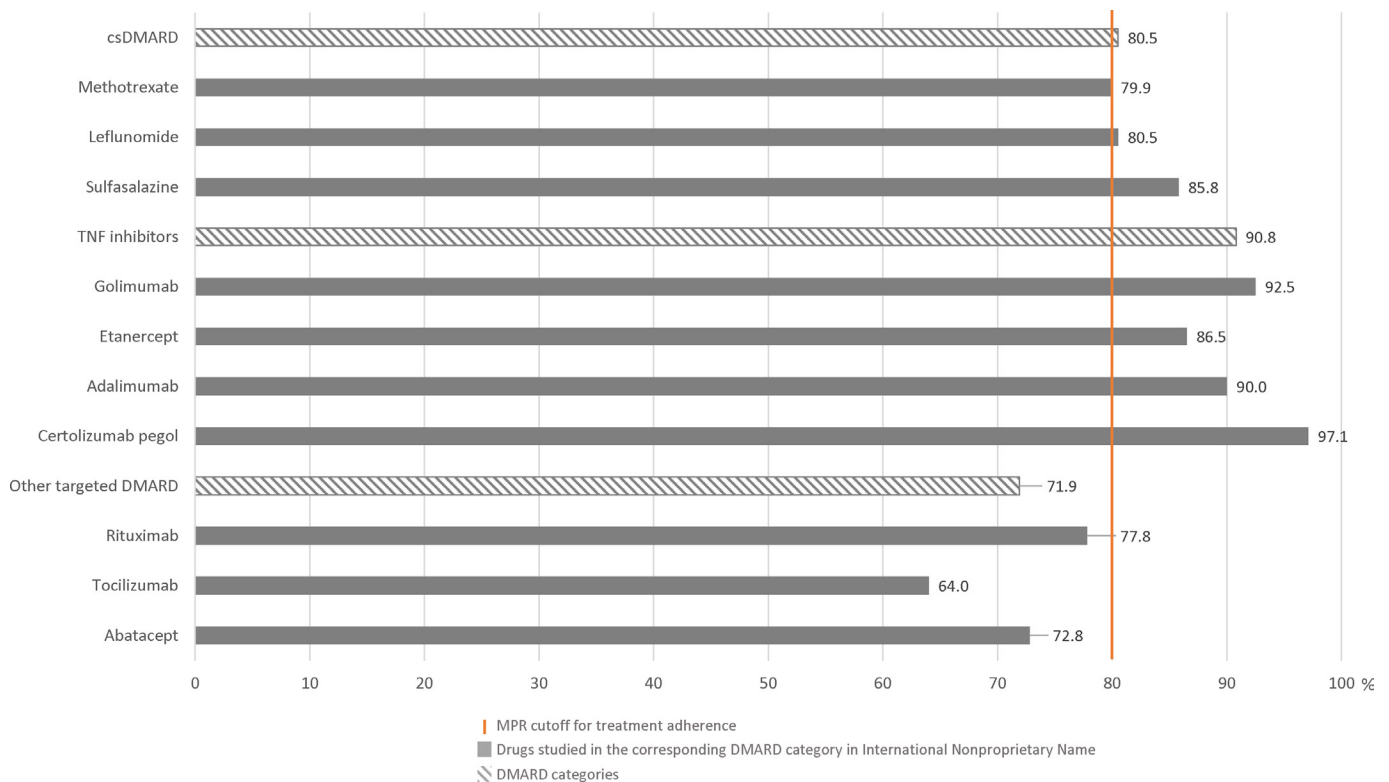


Figure 3 Mean medication possession ratio (MPR) (n=1142). csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; TNF, tumour necrosis factor.

(usually ≤ 5 mg/day for a maximum of 6 months) to avoid adverse events.^{7 27 33} However, this study highlighted an important discrepancy between guidelines and usual practice, as corticosteroids were found to be associated with DMARDs for more than 6 months in 39.7–53.1% of the cases, depending on the DMARD used, with an average daily dose of 6.5–7.8 mg/day prednisone equivalent. The most likely reason for this discrepancy could be that corticosteroids can be prescribed over a long period without re-evaluating their relevance. Crossfield *et al* showed similar results in the UK, with 32.2% of patients receiving long-term steroid therapy.¹²

It is of note that JAKis have only been available in France since 2017, explaining their relative absence in this study. The therapeutic landscape may have changed since this period.

Treatment persistence

Treatment persistence can be used to assess both the overall exposure to DMARDs, which can indicate the application of therapeutic guidelines and the presence of early discontinuations, reflecting potential inadequate responses or intolerance. In this study, within the 12 months following treatment initiation, more than one-third (36.6%) of patients who initiated a csDMARD discontinued their treatment, with a median persistence of 26.7 months, in line with a recent French study in 190 patients with RA.³⁴ Westerlind *et al* showed similar results in Sweden, with a 12-month persistence of 70.0% for methotrexate.³⁵ By comparison, reported methotrexate persistence in the USA is lower, with almost half of patients discontinuing methotrexate within 1 year.³⁶ Differences in the extent to which databases in France and the USA cover the overall population make comparing these results difficult.

For tDMARDs, the 12-month discontinuation rate was around 43%, with a median persistence of around 16 months. A literature review and meta-analysis based on registries and healthcare databases assessed tDMARD discontinuation in RA, with the 12-month discontinuation rate varying between 21% for abatacept and 30% for other monoclonal antibodies.³⁷ This discrepancy can be explained by the use of different definitions for treatment discontinuation and potential differences in the international practices for tDMARDs, notably regarding the co-prescription of methotrexate. Results between European registries included in this review are relatively similar, with a low overall dispersion.

Untreated population

Forty per cent of the study population did not receive any RA-related treatment during the study period. This is in line with the Crossfield *et al* study in the UK, with a rate of 40.4% among more than 40 000 patients.¹² Untreated patients with RA were elderly with high CCI scores, explaining the lack of DMARD prescriptions in this population. Data specifying a therapeutic strategy for RA management in elderly patients are sparse³⁸; however, an

age of ≥ 70 years is a recognised factor for lower DMARD prescription. The more frequent renal or hepatic insufficiency, polymedication (which increases the risk of drug–drug interactions), comorbidities and the increased risk of infection in the elderly population are frequently used to justify the lack of DMARD treatment.^{38–40} Furthermore, a large proportion of untreated elderly patients with RA received symptomatic treatments (NSAIDs, oral corticosteroids or other pain medications). These findings are consistent with data reporting that elderly patients with RA are more often treated with corticosteroids than csDMARDs or tDMARDs. It should be noted that data on over-the-counter symptomatic treatments are not available in the SNDS, which may underestimate the present results. Of note, untreated patients refer to patients who do not receive any DMARD during the selection period; 15% of patients had at least one dispensation of DMARD within the 3 years prior to inclusion. According to data from Crossfield *et al*, 59.6% of patients with RA received at least one DMARD, leaving 40.4% of patients with no background treatment, in line with the findings of this study.¹²

Despite the potential factors limiting use of DMARDs among elderly patients, their replacement by chronic oral corticosteroids, even at low dose, is not recommended and can lead to severe adverse events in a frail and multimorbid population. The risk of infection is drastically increased with corticosteroids, proportional to the daily dose. Claims analysis showed that the 1-year incidence of hospitalised infection increased by 2–10% when using low to high doses of steroids among patients with RA.⁴¹ Similar trends were found by Schenfeld *et al*, demonstrating increased hospitalised infection rates with increasing oral corticosteroid doses.⁴² Several studies in patients with RA were published by the French multicentric cohort ESPOIR, with 10 years of follow-up. Roubille *et al* showed that steroid exposure was more frequent in patients with severe infections ($p=0.009$). High-dose oral corticosteroids were also associated with more frequent cardiovascular disease ($p=0.001$).⁴³ Another ESPOIR Study from Louveau *et al* showed a significant association between recent high-dose oral corticosteroids and the 5-year risk of radiographic RA progression, highlighting a subgroup of initially highly active RA.⁴⁴ These findings highlight an unmet medical need in chronic RA management among elderly patients, potentially tackled by the redefinition of RA guidelines for this age group, notably regarding DMARDs, or by the emergence of new therapies.⁴⁵

Strengths and limitations

The French healthcare system offers universal coverage for nearly 99% of French residents. All reimbursed medical services are captured in the SNDS, making it a suitable tool for epidemiological and population-based medical resource utilisation research. As DMARDs in France cannot be accessed outside of reimbursement, this study presents an exhaustive and precise overview

of RA epidemiology and treatment patterns in France. Despite being limited for rare diseases due to a potential lack of power, EGB provides the same level of granularity concerning treatments and procedures reimbursed. As described, the main limitation of EGB is a potential lack of power due to the 1/97th sampling of the SNDS database. This is of limited impact to RA epidemiology as the study size remains large enough to produce robust and scalable data but could limit the interpretation of some treatment patterns. Nonetheless, the similarity with European data and with RA guidelines supports the robustness of the study results.

Another limitation is the medicoadministrative nature of the database, which does not capture important information on clinical data, besides hospital diagnoses and LDD. An information bias resulting from coding errors may lead to some patients being included in this study despite not having RA. This could occur regardless of the multiple inclusion and exclusion criteria. Some patients from the untreated subgroup may also have been included while not presenting with RA.

The analysis of comorbidities and medical history could have similar limitations due to a lack of coding or coding errors. The use of validated algorithms based on the literature and French Health Insurance mapping of diseases enables this limitation to be reduced by diversifying the sources of information.⁴⁶

Finally, the description of treatment sequences only represents information on the succession of treatments subsequent to the initial treatments identified as the starting point. This implies that patients for whom a targeted DMARD was identified may largely represent prevalent patients, with a failure of first-line treatment such as methotrexate.

Notwithstanding the limitations and potential bias outlined above, this study highlights a medical need that is not fully covered by current therapies, notably in non-responders, intolerant or non-compliant patients. Few data related to JAKis were available during the study period and a study update would allow assessment of the impact of JAKis on RA treatment patterns. In future, improving clinician understanding of RA treatment sequences using large-scale, real-world data may help optimise treatment decisions.

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