Non-adherence and discontinuation rate for oral and parenteral methotrexate: A retrospective-cohort study in 8,952 patients with psoriatic arthritis

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ABSTRACT

Background and aims: Treatment options for PsA, following non-steroidal anti-inflammatory drugs (NSAIDs), include conventional synthetic disease modifying anti-rheumatic drugs (csDMARDS), particularly methotrexate (MTX). The present study was performed to determine the non-adherence and discontinuation rates of different methotrexate (MTX) formulations in psoriatic arthritis (PsA).

Approach and results: We performed a retrospective-cohort study on patients with PsA identified by disease-specific code in the administrative-health-databases of a Northern Italian region (Lombardy) between 2004 and 2015. Subjects were defined as non-adherent if less than 80% of the prescribed MTX dose was taken based on the time between each prescription. Discontinuation rates were calculated using the time between the first and the last MTX prescription over an observation period of 120 months. Among 8952 patients with PsA, 33% were treated with MTX (mean dosage 10 mg/week ± 2.5 mg standard deviation), more frequently (59%) in its parenteral formulation at a 10 mg weekly dosage (35%). Oral glucocorticoids were prescribed to 21% of patients, while non-steroidal anti-inflammatory drugs to 45%. Approximately 37% of patients with PsA were defined as non-adherent to MTX, with the oral formulation associated with an increased risk of non-adherence (hazard ratio 2.08, 95% confidence interval 1.84–2.35, p < 0.001) compared with parenteral 10–15 mg weekly doses. Oral MTX was discontinued in 52% of cases without a significantly increased risk of discontinuation compared to parenteral formulations which, at higher dosages, had a more favorable retention rate.

Conclusion: Oral MTX formulation is associated with a 2-fold risk of non-adherence compared to MTX parenteral route in PsA.

1. Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by numerous clinical manifestations ranging from skin psoriasis to musculoskeletal inflammatory signs. PsA treatment choices depend on the clinical domains involved, as suggested by the most recent recommendations [1,2], and treatment should be started promptly to improve long term outcomes [3] and prevent radiographic progression [4]. Treatment options for PsA, following non-steroidal anti-inflammatory drugs (NSAIDs), include conventional synthetic disease modifying anti-rheumatic drugs (csDMARDS), i.e. methotrexate (MTX), sulfasalazine (SSZ), and leflunomide (LEF), and biologic DMARDs, particularly targeting tumor necrosis factor alpha (TNF) [5], but numerous patients with PsA remain undertreated [6], and limited...
evidence supports the efficacy of csDMARDs [7].

The present study stems from specific limitations to our current understanding of PsA medical treatments. First, a different pharmacodynamic profile characterizes oral and parenteral MTX formulations [8], while the use of this first-line csDMARD faces limited adherence [9] and is frequently interrupted after a short use [10]. Further, the use of NSAIDs is commonly not addressed in clinical studies and may be used in a significant proportion of patients. Lastly, despite not being included in the current treatment recommendations, we are aware that a variable understanding of PsA medical treatments. First, a different pharmacological profile characterizes oral and parenteral MTX formulations [8], while disease duration was calculated from the diagnosis to the end of follow-up for each subject or as of December 31, 2015.

Each PsA case was linked to the medication database and csDMARD, OGC, and NSAIDs prescriptions were retrieved using ATC codes (MTX L01BA01, sulfasalazine –SSZ- A07EC01, leflunomide –LEF- L04AA13, hydroxychloroquine –HCQ- P01BA02; steroids - H02AB*, NSAIDs - M01A*). The dose of MTX was obtained only for subcutaneous or intramuscular formulations and was determined based on the first prescription (accounting for 2 months of treatment) only if a second prescription was also found with the same dosage. We did not take into account drug dosage changes after the second prescription with the same dosage.

As surrogate for patient adherence, we calculated the prescribed drug quantity and time between prescriptions. Suspected non-compliant subjects were defined as “non-adherent” if the time between each prescription exceeded the planned time, with a calculated current dose being less than 80% of the expected prescribed dose. The data only report rates of prescription refills which do not necessarily correspond to drug consumption [11].

Discontinuation rates were calculated using the time between the first and the last drug prescription, between January 1st, 2004 and December 31, 2015.

Data are presented as absolute numbers and percentages; statistical analyses included χ² test and Mann-Whitney as appropriate. Cox regression analysis was used to estimate the hazard ratio for MTX non-adherence and discontinuation rates. All statistical comparisons were two-tailed and statistical significance obtained for p-values <0.05. Statistical analyses were performed using STATA 13 for Macintosh (StataCorp, College Station, TX, USA).

3. Results

A total of 8952 incident PsA cases were recorded between 2004 and 2015 (4503 women – 50%, median age at enrollment 52 years - interquartile range –IQR 42-61 years) with a median disease duration of 4.7 years (IQR 2.2–7.6 years). Oral glucocorticoids were prescribed to 21% (n = 1892) of patients, while NSAIDs were used by 45% (n = 4034) of PsA cases. Of note, 18% of patients were treated with SSZ, while 8% with HCQ and 7% with LEF.

The profile of csDMARD prescription is illustrated in Table 1. MTX was the most commonly used medication as first and subsequent treatment lines (cumulatively 33% of cases) with 59% of patients receiving the parenteral (including either subcutaneous or intramuscular) formulations (Table 1). Parenteral MTX was most frequently prescribed at 10 mg/week dose (35%; mean dose 10 ± 2.5 mg/week), while the dosage for oral MTX could not be retrieved from the database. Non-adherence to MTX treatment was observed in 38% of patients (n = 1108) with oral MTX associated with a significantly higher risk of non-adherence (Hazard ratio-HR 2.11, 95% confidence interval-CI 1.87–2.39, p < 0.001). Parenteral 7.5, 10 and 15 mg weekly doses were associated with a lower risk of non-adherence (HR 0.79, 95% CI 0.63–0.99, p = 0.038; HR 0.62, 95% CI 0.55–0.71, p < 0.001; HR 0.7, 95% CI 0.58–0.85, p < 0.001; respectively) (Fig. 1). When adjusting for demographic and clinical features (sex, age, disease duration), we confirm that oral MTX was associated with increased non-adherence (HR 2.08, 95% CI 1.84–2.35, p < 0.001), while MTX 10 and 15 mg weekly doses were associated with lower rate of non-adherence (HR 0.63, 95% CI 0.55–0.72, p < 0.001; HR 0.69, 95% CI 0.57–0.83, p < 0.001, respectively).

MTX was discontinued in 48% of patients (n = 1387) in any formulation; albeit the frequency of discontinuation was higher for low-dosage MTX (10 mg/week vs. 15–20 mg/week: 53.1%–49.2% vs. 41.3%–34.6%, odds ratio – OR 1.34, 95% CI 1.1–1.64, p = 0.0039), this did not result in an increased risk of discontinuation (7.5 mg/week HR 1.18, 95% CI 0.93–1.46, p = 0.113; 10 mg/week HR 1.06, 95%CI 0.93–1.21, p = 0.384). Oral MTX was discontinued in 52% of cases (n = 612), but no increased risk of discontinuation was observed compared to parenteral formulations (HR 1.0, 95%CI 0.88–1.12, p = 0.962).

4. Discussion

Taking advantage of the administrative data from a 10-million subject population from Lombardy, a Northern Italian region, and identifying nearly 9000 PsA cases, we report that MTX is the most frequently prescribed csDMARD in this setting, generally at weekly doses equal to or below 15 mg. We also report for the first time that the oral MTX formulation is associated with an increased risk of non-adherence, although we could estimate the weekly doses only for the parenteral formulations.

While the GRAPPA recommendations [1] do not provide a preference for a specific csDMARD, EULAR support MTX as the csDMARD of choice for PsA [12]. The evidence supporting the use of MTX is gathered from data in rheumatoid arthritis, with few studies addressing its efficacy in PsA [13–15], more recently in real-life [16]. We herein confirm that MTX is the most commonly prescribed csDMARD, in particular in

Table 1

| Synthetic csDMARDs prescription patterns in the Lombardy region. The dosage of oral MTX was not available for analysis. |
|---------------------------------------------------------------|
| MTX, n (%) | Oral, n (%) |
| 7.5 mg/week, n (%) | Parenteral |
| 10 mg/week, n (%) | 273 (9.25%) |
| 15 mg/week, n (%) | 1032 (35%) |
| 20 mg/week, n (%) | 407 (13.8%) |
| >20 mg/week, n (%) | 26 (0.9%) |
| SSZ, n (%) | 1641 (18%) |
| LFN, n (%) | 653 (7%) |
| HCQ, n (%) | 715 (8%) |
| OGC, n (%) | 1892 (21.1%) |

Abbreviations: MTX, methotrexate; SSZ, sulfasalazine; LFN, leflunomide; HCQ, hydroxychloroquine; OGC, oral glucocorticoids
the parental formulation. We suggest that the low rate of LEF prescriptions may be secondary to its relatively recent availability during the considered decade [17,18], while we note that the use of HCQ in PsA is not evidence-based nor endorsed by current recommendations.

The applicability in everyday practice of data from randomized clinical trials may be limited by stringent exclusion and inclusion criteria [19], thus making population-based real-life studies of growing importance [20]. In this view, drug retention rates are used as an indirect indicator of overall treatment effectiveness and safety in observational studies and administrative databases. We herein report that MTX discontinuation rate between 2004 and 2015 is about 50%, thus confirming the efficacy and good tolerability of this treatment. Overall, parental MTX at higher dosages seems to have a more favorable retention rate, suggesting a higher efficacy, as recently shown in the TICOPA study [21]. The effectiveness of treatments is generally burdened by the frequently low-adherence in real-life. In our cohort derived from administrative databases we found that approximately 37% of patients with PsA are non-adherent to MTX therapy and we may consider this as expected due to the common adverse effects, particularly nausea and vomiting, rather than the efficacy. More importantly, the choice of MTX route of administration may improve adherence [22], which is lower in patients treated with the oral formulation, possibly due to the digestive intolerance, as previously reported [23]. Thus, the use of middle-dose parenteral MTX in PsA should be advised, also considering the higher availability reported in recent studies [24] while lowering doses does not impact on adherence after controlling for confounding factors. Unfortunately, it is not possible to obtain additional drug adherence information as we do not have patients’ specific clinical data or drug prescription information.

The present study addresses for the first-time the prescription patterns in PsA patients in the Lombardy region in Italy. We note that the analysis of administrative-health databases in a National health system is the ideal setting to accurately evaluate prescription patterns and treatment adherence, even though with two main limitations: it provides only a surrogate of the real-life setting, and it lacks detailed clinical information while possibly under-representing milder cases of PsA. An important aspect of our study is that the analyzed patients are representative of the general population, including subjects followed at centers with different levels of referral. A possible objection may be that rheumatoid arthritis patients may have been misclassified as PsA, as this may supported by the high prescription rates for OGC and HCQ, but this aspect does not seem to be relevant considering that exemptions codes for rheumatoid arthritis are more inclusive (and thus may be preferred by patients and physicians) compared to PsA. We are also well aware of other study limitations, such as the lack of validation of the PsA diagnosis or the missing clinimetric data with the latter being estimated by the use of NSAIDs or steroids. Additional limitations are represented by the lack of updated analysis from 2015 and the lack of data related to the use of biologics concomitant with MTX. It is not possible to go back to individual clinical cases for further analysis of aspects such as the reason why MTX was chosen, stopped or discontinued, if this was due to side effects, loss of effectiveness, fear of the patient for potential side effects, as these aspects are not included in the analyzed database.

Moreover, biologics are not included in the present study as these drugs are distributed directly by referral hospitals and are not in the utilized databases. The account of biologic therapies in our analysis is expected to significantly influence the dose and use of MTX and other DMARDs in combination treatments, although this is generally considered to be less relevant in PsA or other spondyloarthritides compared to rheumatoid arthritis [25,26]. This limitation could explain the surprisingly high percentage of PsA patients treated with low dose MTX, such as 10 mg/week.

5. Conclusions

We report that MTX is the most commonly prescribed csDMARD in PsA and that MTX non-adherence is a very frequent issue in everyday practice, particularly when the oral formulation is chosen. Our analysis was performed in the years 2004–2015 because data were complete and available only for this timeframe, and we are aware that longer follow-up with additional information on biologic use in combination with MTX is of high relevance. Besides this fundamental aspect to be considered, future developments may also include the analysis of sex differences in MTX use, and a more detailed history of OGC and NSAIDs

![Image](image-url)
use. In fact, the use of OGC in 21% of PsA cases, albeit clinically unjustified and possibly relevant to the excess mortality associated with PsA [27], seems consistent with figures reported from a large registry [28] while the use of NSAIDs in 45% of cases poses obvious concerns in terms of safety and the underuse of alternative safer long-term options. We are currently in an era in which several biologics are available for PsA, including anti-TNF (originators and biosimilars), IL17, IL12/23, PDE4, and understanding how to manage MTX tolerability and efficacy is still of pivotal importance to reach disease remission in combination therapies.

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