Long-term safety of combination treatment with methotrexate and tumor necrosis factor (TNF)-α antagonists versus TNF-α antagonists alone in psoriatic patients

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Abstract
Methotrexate, a folic acid analog, is the conventional systemic anti-psoriatic agent most commonly chosen for combination with biologics in the treatment of psoriasis. Real-world long-term safety data of this combination versus biologic treatment alone in dermatological practice are sparse. Here, we present results of a comparative retrospective study of laboratory dynamics and adverse events in psoriatic patients receiving a tumor necrosis factor (TNF)-α antagonist (adalimumab or etanercept) with and without concomitant methotrexate (176 treatment courses, mean duration of 629 days). Co-treatment with methotrexate significantly ($P < 0.05$) correlated with a decrease of leukocyte, neutrophil and erythrocyte counts and an increase of glutamate pyruvate transaminase (GPT) (Pearson correlation, $n > 148$). The relative risk for a Common Terminology Criteria for Adverse Events (CTCAE) grade 1–2 laboratory adverse event was significantly elevated to 1.11 for anemia and 1.16 for a GPT increase if the patients received concomitant methotrexate at the time the laboratory test was performed. Combination treatment was given for equal or more than 30% of the time ($MTX_{\geq 30\%}$) during 12% of the treatment courses. During these treatment courses, dynamics of leukocyte (~8.1%), neutrophil (~8.1%), erythrocyte (~3.2%) counts and GPT (~16.9%) from baseline to average under treatment were significantly more pronounced. CTCAE grade 3–4 laboratory adverse events occurred in 9.5% and 5.2% of treatment courses with and without $MTX_{\geq 30\%}$, respectively ($p = 0.70$), and affected transaminases in 90% of the cases. Methotrexate was discontinued due to CTCAE grade 3–4 laboratory adverse events in 4.25% of the treatment courses with MTX of 30% or more. Elevated baseline γ-glutamyl transferase levels significantly predicted the occurrence of CTCAE grade 3–4 laboratory adverse events and should trigger investigations for pre-existing liver disease or alcohol abuse.

In conclusion, our comparative data supplement previous short-term studies and support a tolerable long-term safety profile of the combination treatment. However, given the additional toxicities and low evidence for benefits, alternative options such as biologic monotherapy or switching to a different biologic should be considered in a dermatological setting.

Keywords
adalimumab, etanercept, methotrexate, psoriasis, safety
1 | INTRODUCTION

Adalimumab, a humanized direct tumour necrosis factor (TNF-α) antagonist, and etanercept, a soluble decoy receptor for TNF-α, were first introduced to the treatment of psoriasis more than 10 years ago and are still commonly prescribed and high-sales biologics. According to a recent review, combination treatments of biologics with methotrexate (MTX) account for as many as 7% of biologic treatments in a dermatological setting. Among the most common reasons for combination treatment were insufficient response to the biologic treatment alone, concomitant psoriatic arthritis and the prospect to reduce immunogenicity. However, combination treatment with TNF-α antagonists and MTX is not officially approved for psoriasis by the drug regulation agencies in the USA, Europe and Japan, and alternative options such as switching to a different biologic are available. Therefore, it is crucial to critically assess the risks and benefits of combination treatment versus treatment with a biologic alone. Unfortunately, while substantial safety data for the combination treatment of rheumatoid and psoriatic arthritis with TNF-α antagonists and MTX is available, respective data for the treatment of psoriasis in a dermatological setting – and in particular comparative safety data of combination treatment versus treatment with a biologic alone – is very limited.

Based on a systematic review from 2015, supplemented by a PubMed search for relevant articles in subsequent years (see Methods section), only four studies reported comparative safety data for the combination of etanercept and MTX, and only one study reported comparative safety data for the combination of adalimumab and MTX. All of the studies were limited to a follow up of 24 weeks and only one study reported “real-world” observational data. However, combination treatment with a TNF-α antagonist and MTX is usually administrated for a much longer time and safety data from studies with defined inclusion criteria can vary to real-world conditions. Extrapolation of data from rheumatological to dermatological patients is error prone. Prescription practices, in particular the common approach to initiate MTX either before or simultaneously with a biologic under rheumatological guidance, and, with respect to rheumatoid arthritis and psoriasis, comorbidities, in particular the increased incidence of non-alcoholic steatohepatitis in psoriasis, differ considerably. Therefore, additional comparative long-term real-world safety data of combination treatment versus treatment with a biologic alone in a dermatological setting is highly desirable.

Here, we report a real-world long-term retrospective cohort study of psoriatic patients treated in a dermatological tertiary care clinic to compare laboratory dynamics and laboratory adverse events as robust safety criteria under treatment with one of the TNF-α antagonists adalimumab and etanercept alone and in combination with MTX to further address this matter.

2 | METHODS

2.1 | Patients

Patients were eligible for study participation if they were treated with adalimumab or etanercept for psoriasis at the Department of Dermatology, University of Heidelberg, if they provided written informed consent for retrospective data analysis, and if relevant laboratory data was available for at least one of the biologics. Data was extracted from patient records and stored in an SPSS database for further analysis (IBM, Armonk, NY, USA). A treatment course encompassed the interval from initiation to termination of a specific treatment. Patients consecutively treated with adalimumab and etanercept could contribute data to both biologics. If treatment with a given biologic was, however, terminated for any reason and re-initiated later, only the first treatment course was eligible. Three hundred and fifty-six patient records were screened and 176 eligible treatment courses from 142 patients were identified. This study was approved by the institutional review board of the University of Heidelberg and conducted in accordance with the Declaration of Helsinki.

2.2 | Literature search

A PubMed search with the search string “psoriasis AND methotrexate AND (adalimumab OR etanercept) AND safety” was performed (date accessed 14 September 2020) to identify relevant studies published between 2015 and 2020 to supplement data reported in a systematic review from 2015. Sixty-three articles were found. Titles and abstracts were screened to assess whether relevant data was reported, and selected manuscripts were reviewed in full text. As in van Bezoijen et al., papers solely reporting data from psoriatic arthritis patients were excluded.

2.3 | Standard treatment schemes and clinical status

Typically, 40 mg adalimumab is administrated s.c. every other week after an initial loading dose of 80 mg. Etanercept is administered s.c. with an initial dose of 25–50 mg biweekly or 25 mg weekly for 12 weeks followed by biweekly administration of 25 mg or weekly administration of 50 mg following national guidelines. Routine visits including laboratory tests are usually scheduled every 8–12 weeks. MTX is administrated at doses of 10–15 mg/week, usually s.c., followed by 5 mg folic acid p.o. 24 h later. The presence of psoriatic arthritis, cardiovascular, metabolic and pulmonary comorbidities were retrieved from the patient charts as documented by the treating physician (i.e. arterial hypertension, coronary heart disease, chronic obstructive lung disease, diabetes mellitus, hyperlipidemia, hyperuricemia, documented obesity).
2.4 | Laboratory tests

Laboratory blood tests are routinely performed at follow-up visits every 6–12 weeks in psoriatic patients receiving adalimumab and etanercept. Measurements of routine laboratory parameters were accepted as baseline values up to 30 days prior to treatment initiation, if no biologic treatment was administered during this period. Laboratory adverse events were defined as 1–2 and 3–4 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf; Table S1).

2.5 | Statistics

The primary end-point of the present study was to assess the two-sided Pearson correlation between MTX co-treatment (percentage of time) and routine parameter baseline-to-treatment ratios (numerator, average under treatment value; divisor, baseline value). Patients were divided into those with concomitant treatment with MTX for less versus equal or more than 30% of the time and routine parameter baseline-to-treatment ratios were compared between the groups (two-sided Mann–Whitney U-test). A two-sided \( \chi^2 \)-test was used to assess whether the occurrence of CTCAE graded laboratory adverse events depended on concomitant MTX treatment at the time of occurrence. A two-sided Fisher’s exact test was used to compare the occurrence of CTCAE grade 3–4 laboratory adverse events between patients with concomitant MTX treatment for less versus equal or more than 30% of the time. Two-Sided Student’s t-tests, Mann–Whitney U-tests and Fisher’s exact tests were used as appropriate to compare patient characteristics between patients who did and did not experience a CTCAE grade 3–4 laboratory adverse events. A binary logistic regression analysis was performed to assess whether patient characteristics, baseline laboratory values or MTX co-treatment predict CTCAE grade 3–4 laboratory adverse events. Power was calculated using G*power 3.1.9.2.\(^2\)

Values are given as mean and standard deviation, if not specified otherwise. \( p < 0.05 \) was considered significant. Statistical procedures were performed using SPSS version 22.0.

3 | RESULTS

3.1 | Study population

One hundred and seventy-six treatment courses (113 adalimumab, 63 etanercept) with a mean duration of 89.9 ± 82 weeks were included. This corresponds to 303 patient-years under treatment. Between 1916 and 2169 test results were available for each laboratory parameter during this time. Fifteen percent of treatment courses involved combination treatment with MTX at some point. Patients already received MTX when biologic treatment was commenced or both treatments were started simultaneously in 42% of these cases. Patients received combination treatment with MTX for equal or more than 30% of the time in 12% of the cases (average duration of combination treatment in these patients, 76.5 ± 50 weeks). Patient characteristics are summarized in Table 1.

3.2 | MTX co-treatment and routine laboratory parameter dynamics

Table 2 shows the Pearson correlation coefficients between MTX co-treatment (percent of time) and routine laboratory parameter baseline-to-treatment ratios. A significant negative correlation was found between MTX co-treatment and leukocyte, neutrophil and erythrocyte counts, and a significant positive correlation was found between MTX co-treatment and glutamate pyruvate transaminase (GPT) concentrations. To further assess these observations, treatment courses were divided into those with MTX co-treatment for less and those with MTX co-treatment for equal or more than 30% of the time. Patient characteristics of both groups are shown in Table 1.

### Table 1: Patient characteristics

| MTX co-treatment | <30% | ≥30% |
|------------------|------|------|
| Number           | 176  | 155  | 21   |
| Adalimumab       | 113  | 95   | 18   |
| Etanercept       | 63   | 60   | 3    |
| Age (years), mean ± SD | 47.1 ± 13  | 47.3 ± 13 | 45.6 ± 12 |
| Sex (male)       | 63.6%| 65.8%| 47.6%|
| Plaque-type psoriasis | 93.8%  | 93.5%| 95.2%|
| Pustular psoriasis | 6.3%  | 6.5% | 4.8% |
| Previous systemic treatments, mean ± SD | 2.7 ± 1.4  | 2.7 ± 1.4 | 2.6 ± 1.5 |
| Psoriatic arthritis | 47.2%  | 45.2%| 61.9%|
| Concomitant treatment with MTX (% of time), mean ± SD | 9.9 ± 27  | 0.3 ± 2 | 80.1 ± 23 |
| Cardiovascular, pulmonary or metabolic comorbidity | 40% | 41% | 33% |
| Baseline PASI, median [IQR] (n) | 9.2 [5–14] (162) | 9.4 [6–14] (141) | 8.4 [5–14] (21) |
| Treatment duration (days), mean ± SD | 629 ± 576 | 624 ± 594 | 669 ± 439 |

Abbreviations: IQR, interquartile range; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; SD, standard deviation; TNF-\( \alpha \), tumor necrosis factor-\( \alpha \).

\( ^a \)Percent of time.
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(Mann–Whitney U-test). Table S2 compares baseline-to-treatment ratios for selected parameters depending on MTX co-treatment and the presence or absence of psoriatic arthritis. Except for neutrophil counts, which decreased more under MTX co-treatment in psoriatic arthritis patients, dynamics were comparable.

3.3 MTX co-treatment and laboratory adverse events

To assess whether MTX co-treatment results in laboratory adverse events, the occurrence of laboratory abnormalities, graded according to the CTCAE, among leukocyte, neutrophil counts, hemoglobin and transaminases were investigated. Table 4 shows the distribution of normal laboratory values, CTCAE grade 1–2 and 3–4 laboratory adverse events depending on the presence of MTX co-treatment at the time the laboratory test was performed. Between 2123 and 2167 laboratory test results were available for each category. CTCAE grade 1–2 anemia and GPT increase were significantly more common if patients received concomitant MTX co-treatment (two-sided $\chi^2$-test).
Adverse events of CTCAE grade 3–4 occurred in two treatment courses (9.5%) with combination treatment for equal or more than 30% of the time and these events are detailed in Table 5. In both cases, transaminases were increased. In one case, the increase was attributed to alcohol intake and MTX was continued; in the other case, the increase was attributed to MTX co-treatment and transaminases normalized after cessation of MTX. CTCAE grade 3–4 laboratory adverse events occurred in eight treatment courses (5.2%) with combination treatment for less than 30% of the time (one, neutropenia; one, glutamate oxalacetaate transaminase increase; three, GPT increase; three, γ-glutamate transaminase [GGT] increase). Two patients who were subsequently treated with adalimumab had CTCAE grade 3–4 GGT increases already at baseline and were excluded. Biologic treatment was discontinued in two of the cases with CTCAE grade 3–4 liver enzyme elevations, one due to subsequent detection of hepatic metastases and one with concomitant hemochromatosis in good skin condition. The occurrence of CTCAE grade 3–4 adverse events was not significantly different between either group (MTX ≥ 30% vs MTX < 30%; 9.5% vs 5.2%, p = 0.697, n = 175, two-sided Fisher’s exact test). The intervals between laboratory tests did not differ between either group (MTX ≥ 30% vs MTX < 30%; 44 ± 13 vs 45 ± 37 days, n = 21 vs 155, p = 0.921, Student’s t-test). Table 6 shows characteristics of patients who experienced CTCAE grade 3–4 laboratory adverse events. While the proportion of patients receiving MTX of more than 30% was higher in the CTCAE grade 3–4 group, the difference was not significant. However, elevated baseline transaminase levels, in particular baseline GGT, were associated with the occurrence of CTCAE grade 3–4 laboratory adverse events. Table S3 shows the same parameters as Table 6 for patients who received MTX for less and equal or more than 30% of the time, separately. In both groups, elevated baseline transaminase levels were associated with CTCAE grade 3–4 laboratory adverse events. Table S4 shows results of a binary logistic regression analysis to identify independent predictors of CTCAE grade 3–4 laboratory adverse events. CTCAE grade 1 or more baseline GGT elevations were a significant predictor. MTX co-treatment for equal or more than 30% of the time, the presence of cardiovascular, pulmonary or metabolic comorbidity, and psoriatic arthritis did not significantly predict the occurrence of CTCAE grade 3–4 laboratory adverse events.

3.4 | Power

The study achieved at least 80% power to detect a small-to-medium effect size correlation in the Pearson correlation analyses given in Table 2 (n = 107, 0.26; n = 140: 0.23) with α = 0.05. The study achieved at least 95% power to detect a small effect size (ω < 0.08) in the χ²-test analyses presented in Table 4 with α = 0.05.

4 | DISCUSSION

The present study provides a long-term comparative analysis of laboratory parameter dynamics and laboratory adverse events under MTX and TNF-α antagonist co-treatment in psoriatic patients under real-world conditions and dermatological guidance.

Our data show that, compared with treatment with a TNF-α antagonist alone, MTX co-treatment resulted in decreased leukocyte, neutrophil and erythrocyte counts and increased GPT. The relative risk to experience CTCAE grade 1–2 anemia and GPT increase was increased under MTX co-treatment by 11% and 16%, respectively. While CTCAE grade 3–4 laboratory adverse events were more common under MTX co-treatment by 9.5% versus 5.2%, the difference was not significant. Among the patients with MTX co-treatment, MTX had to be discontinued due to a CTCAE grade 3–4 laboratory adverse event in 4.25%. Alcohol abuse or unrelated liver disease (hemochromatosis) were identified in 12.5% and 50% of patients with CTCAE grade 3–4 laboratory adverse events on MTX co-treatment for less and equal or more than 30% of the time, respectively, and might have been present occultly already at baseline. Indeed, CTCAE grade 1 or more baseline GGT elevations, which may result from conditions including alcohol abuse, obesity or hypertriglyceridemia, significantly predicted the occurrence of CTCAE grade 3–4 laboratory adverse events.

**TABLE 4** Distribution of normal laboratory values and CTCAE laboratory adverse events depending on methotrexate co-treatment at the time of occurrence

| CTCAE Category | MTX co-treatment | Relative Risk | Sig. |
|----------------|------------------|---------------|------|
|                | No | Yes |               |      |
| Leucopenia     | 0  | 96.4% | 98.7% |       |
| 1-2            | 3.6% | 1.3%  | 0.98  | 0.085 |
| 3-4            | 0.0%  | 0.0%  | n.a.  | n.a.  |
| Neutropenia    | 0  | 99.1% | 100.0% |       |
| 1-2            | 0.8%  | 0.0%  | 0.99  | 0.309 |
| 3-4            | 0.1%  | 0.0%  | 1.00  | 0.215 |
| Anemia         | 0  | 97.2% | 87.4% |       |
| 1-2            | 2.8%  | 12.6% | 1.11  | 0.000*|
| 3-4            | 0.0%  | 0.0%  | n.a.  | n.a.  |
| GOT increase   | 0  | 86.4% | 82.6% |       |
| 1-2            | 13.5% | 17.4% | 1.05  | 0.132 |
| 3-4            | 0.1%  | 0.0%  | 1.00  | 0.211 |
| GPT increase   | 0  | 61.9% | 53.3% |       |
| 1-2            | 37.8% | 46.3% | 1.16  | 0.011*|
| 3-4            | 0.4%  | 0.4%  | 1.00  | 0.899 |
| GGT increase   | 0  | 70.8% | 71.1% |       |
| 1-2            | 26.9% | 25.1% | 0.98  | 0.610 |
| 3-4            | 2.3%  | 3.8%  | 1.02  | 0.269 |

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; GGT, γ-glutamate transaminase; GOT, glutamate oxalacetaote transaminase; GPT, glutamate pyruvate transaminase; MTX, methotrexate; Sig., significance, χ²-test.

*At the time of occurrence.

*p < 0.05.
laboratory adverse events. These patients may require a more extensive work-up and follow up and, ultimately, may be less suited to MTX co-treatment.

In contrast to studies exclusively focusing on combination treatment, comparative real-world data allow a more reliable assessment of additional risks conveyed by MTX co-treatment versus treatment with a TNF-α antagonist alone. While the only previously available study reporting real-world comparative safety data had a follow up of 24 weeks,16 the average duration of combination treatment in the present study was considerably longer at 76.5 weeks. Thus, our data substantially expand the available body of evidence.

Similar to our findings, the most common adverse events under combination treatment in previous studies were liver enzyme elevations and largely attributed to MTX.12,14,22 Indeed, myelosuppression and liver enzyme abnormalities are well-known adverse events in psoriatic patients under treatment with MTX.23 In the largest study to date, a randomized controlled trial by Gottlieb et al.14 with 239 patients over 24 weeks, the most common laboratory abnormality considered an adverse event was a GPT increase with an absolute risk of 2.5% versus 1.3% in the group with and without MTX co-treatment, respectively. The absolute risk to experience a CTCAE grade 3–4 GPT increase due to MTX co-treatment in the present study was 4.8%. This number is comparable to the 5.7% (6/104) absolute risk to develop a CTCAE grade 3–4 GPT increase previously reported for psoriasis and psoriatic arthritis patients on long-term MTX treatment alone.24

### Table 5: CTCAE grade 3–4 laboratory adverse events in patients under combination treatment with methotrexate and adalimumab or etanercept for 30% or more of the time

| CTCAE 3–4 adverse event | Biologic | Occurrence (day) | MTX cessation | Comment |
|-------------------------|----------|-----------------|---------------|---------|
| GPT increase            | ADA      | 737             | Yes           | Once 239 U/L, fell to normal limits after cessation of MTX |
| GGT increase            | ETA      | 28              | No            | Repeatedly increased up to 523 U/L, high alcohol intake, MTX continued |

Abbreviations: ADA, adalimumab; CTCAE, Common Terminology Criteria for Adverse Events; ETA, etanercept; GGT, γ-glutamate transaminase; GPT, glutamate pyruvate transaminase; MTX, methotrexate.

### Table 6: Characteristics of patients who experienced CTCAE grade 3–4 laboratory adverse events

| CTCAE grade 3–4 | No | Yes | Sig. |
|-----------------|----|-----|------|
| Number          | 166| 10  |      |
| Age (years), mean ± SD | 47.1 ± 13 | 47.2 ± 13 | 0.974* |
| Sex (male)      | 63.9% | 60.0% | 1.000** |
| Previous systemic treatments, mean ± SD | 2.7 ± 1 | 3.0 ± 2 | 0.434* |
| Psoriatic arthritis | 46.4% | 60.0% | 0.520** |
| Concomitant MTX ≥30% of the time | 11.4% | 20.0% | 0.340** |
| Cardiovascular, pulmonary or metabolic comorbidity | 37.4% | 60.0% | 0.188** |
| Treatment duration (days), mean ± SD | 623 ± 582 | 722 ± 485 | 0.599* |
| Baseline GOT, median [IQR] (n) | 29.02 [20–39] (141) | 45.52 [25–54] (10) | 0.010† |
| Baseline GPT, median [IQR] (n) | 20.02 [16–26] (141) | 24.52 [22–60] (10) | 0.070† |
| Baseline GGT, median [IQR] (n) | 25.02 [19–39] (141) | 63.52 [21–167] (10) | 0.035† |

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; GOT, glutamate oxalacetate transaminase; GPT, glutamate pyruvate transaminase; IQR, interquartile range; MTX, methotrexate; SD, standard deviation; Sig., significance.
*Student’s t-test
**Fisher’s exact test.
†Mann–Whitney U-test.
treatments with MTX and etanercept or adalimumab were discontinued because of adverse events. However, these events were not further characterized in the latter study, it is unknown which drug was discontinued and no comparative analysis was done. Overall, our data is also generally in line with data from rheumatoid and psoriatic arthritis patients, where no additional safety signals were found for combination treatment with adalimumab or etanercept and MTX compared with each drug alone.4–7,9,10

Data on the benefits of and guideline recommendations for combination treatment with TNF-α antagonists and MTX in psoriasis and psoriatic arthritis are heterogeneous. While combination treatment in psoriatic arthritis is recommended by the European League Against Rheumatism based on evidence for a reduction of immunogenicity,19,26–28 biologic monotherapy of psoriatic arthritis is recommended over combination therapy by the American College for Rheumatology and National Psoriasis Foundation.29

While a superior efficacy of etanercept and MTX versus etanercept alone was noted in a randomized controlled trial of psoriatic patients over 24 weeks,14 a recent review of registry data suggested that drug survival of combination treatment was similar to drug survival of biologic monotherapy.3 As expected from the lack of robust evidence for benefits and sparse comparative long-term safety data in a dermatological setting, no strong recommendations concerning combination treatment are given in the current dermatological psoriasis guidelines from Europe, the USA and Japan.27,28,30 Therefore, even though our data support a tolerable long-term safety profile of the combination treatment, alternative options such as biologic monotherapy or switching to a different biologic should be considered.

4.1 Generalizability, power and study limitations

Although limited by its retrospective design, the strengths of this study are its real-world setting, the description of parameter dynamics at a high temporal resolution and the long observation period. Sex, age and Psoriasis Area and Severity Index (PASI) of our study population are comparable to registry data reported for psoriatic patients under systemic treatment in Germany.31 Patients with MTX co-treatment for equal or more than 30% of the time were less likely to receive etanercept compared with adalimumab. However, routine laboratory parameter dynamics were previously shown to be mild, mainly affect markers of systemic inflammation and not to differ between either biologic.22,33 Patients under MTX co-treatment were more likely to have concomitant psoriatic arthritis. Due to sample size restrictions, no detailed subgroup analyses of psoriatic patients with and without psoriatic arthritis were performed, multivariate analyses suggest that psoriatic arthritis has no significant impact on the occurrence of CTCAE grade 3–4 laboratory adverse events. Previous data indicate that the toxicity of MTX monotherapy does not differ between patients with psoriasis and psoriatic arthritis.34–36 The percentage of patients with psoriatic arthritis under combination treatment in the present study is strikingly similar to data reported from dermatological registry data (61.9% and 62.5%, respectively).3 All patients included in the present study were treated in a dermatological tertiary care clinic. Thus, similar to patients without arthritis, patients with concomitant arthritis had considerable cutaneous disease and reflect the population encountered by dermatologists (baseline PASI 8.6 [median], 4–12 [interquartile range], n= 78). Cardiovascular, pulmonary or metabolic comorbidity were slightly less common in the group that received MTX for equal or more than 30% of the time. While MTX co-treatment and cardiovascular, pulmonary or metabolic comorbidity did not significantly predict the occurrence of CTCAE grade 3–4 laboratory adverse events in a multivariate analysis in the present study, significance might have been missed given the broad confidence intervals. Potential additional confounders such as body mass index, which might have influenced the decision of the treating physician to initiate MTX, cannot be completely controlled for in the present retrospective setting. The present study was sufficiently powered to detect a small-to-medium effect size correlation with 80% probability in the Pearson correlation analyses and to detect a small effect size with 95% probability in the χ2-test (see Results section).

Our data supplement previous short-term comparative safety data and suggest that co-treatment of psoriatic patients with TNF-α antagonists and MTX in a dermatological setting has expected additional laboratory toxicities compared with treatment with a TNF-α antagonist alone. No new safety signals were detected. Even though our data therefore support a tolerable long-term safety profile of the combination treatment, its additional toxicities and low evidence for benefits suggest that alternative options such as biologic monotherapy or switching to a different biologic should be considered in a dermatological setting.

CONFLICT OF INTEREST

None declared.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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