BRIEF ARTICLE

Methotrexate Monitoring in Dermatology: A Follow-Up Retrospective Cohort Study

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INTRODUCTION

Methotrexate is an immunosuppressive medication approved by the FDA in 1972 for treatment of severe, recalcitrant psoriasis.[1] `As there have been no large-scale, high-quality studies on the efficacy and safety of methotrexate[1], guidelines regarding methotrexate treatment were written and revised based largely on expert opinion.

Prior research by our team investigated whether certain monitoring practices or baseline patient characteristics were associated with lab abnormalities resulting in clinically relevant events (CREs) within the first 90 days of methotrexate treatment. CREs were defined as when abnormal lab studies resulted in: 1) methotrexate dose being decreased, 2) methotrexate dose not being increased as intended 3) methotrexate being discontinued or 4) repeat testing being ordered. We concluded that dermatologists may consider postponing lab monitoring until 15 days following methotrexate initiation.[2]

This follow-up study was performed to determine when within the first 90 days of treatment CREs were most likely to occur and define the specific values at which abnormal labs resulted in a CRE. This should provide additional evidence-based suggestions for methotrexate laboratory monitoring.

METHODS

Records of 243 dermatology patients at University of Virginia Health System from 1/1/2013 to 12/31/2019 were retrospectively reviewed. Exclusion criteria included: methotrexate not prescribed by a dermatologist, patient lost to follow-up, baseline labs not drawn, or insufficient documentation. Data collected included initial lab values, specific values of abnormal labs, and dates of lab draws. Labs were considered abnormal if outside of predetermined laboratory reference ranges. All statistical analyses were performed using R. Descriptive statistics, including frequencies and percentages, were calculated for all laboratory tests per week. The weekly percentage of CREs per total number of labs drawn was graphed. Average values of abnormal lab tests associated with and without CREs were calculated and compared via t-test.

RESULTS

A total of 243 patients and 374 laboratory values were analyzed. The percentage of CREs per weekly lab draw was plotted (**Figure 1**). Compared to other weeks, week 11 had the highest percentage of CREs (11.1% vs 2.3%, p = .00003), with slight
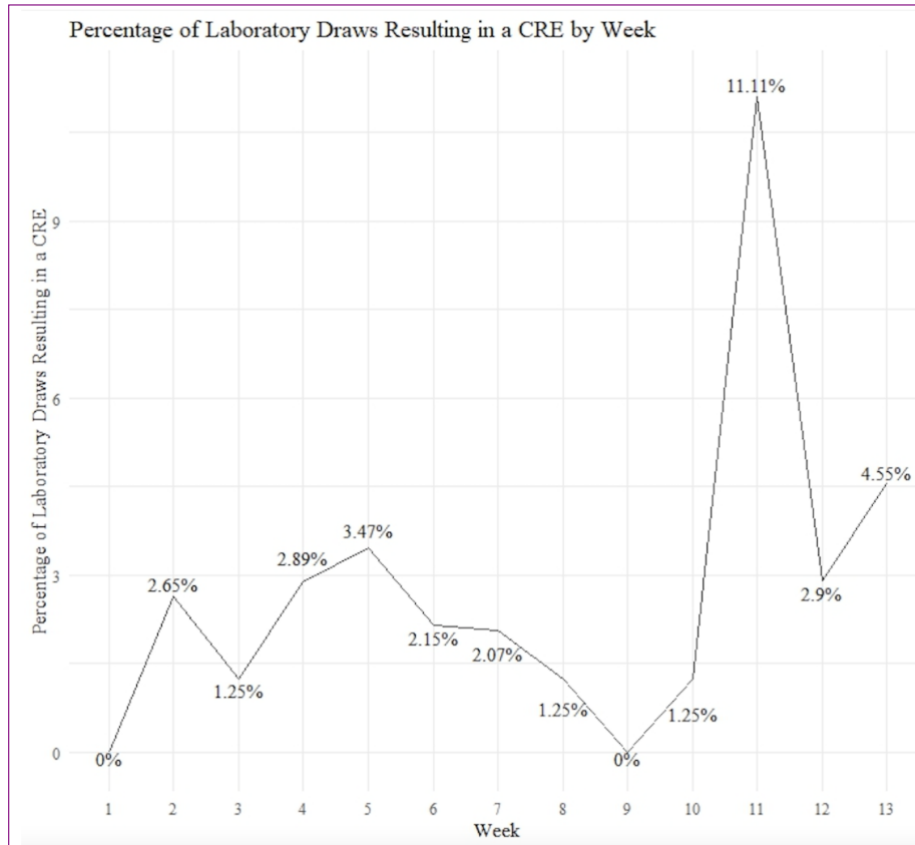
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Figure 1. Rate of CREs per week as a percentage of all laboratory tests per week.

Laboratory Test (Reference Range)	Mean (CRE)	Mean (No CRE)	P-value
AST (0-34 U/L)	53.5	41.3	0.03*
ALT (0-34 U/L)	103	50.5	0.00087***
AP (36-92 U/L)	174	144	0.73
Creatinine (0.5-1.2 mg/dL)	1.4	1.33	0.7
Lymphocyte Count (below 1-2.9 x 10^9/L)	0.629	0.726	0.29
Hemoglobin (13-17 g/dL)	11.8	12.4	0.79
White Blood Cell Count (above 4.5-11 x 10^9/L)	14.3	11.7	0.39
White Blood Cell Count (below 4.5-11 x 10^9/L)	2.96	3.89	0.19
Platelets (above 150-450 x 10^9/L)	474	403	N/A
Platelets (below 150-450 x 10^9/L)	105	134	0.19
Absolute Neutrophil Count (above 2.5-6 x 10^9/L)	9.7	7.23	0.38
Absolute Neutrophil Count (below 2.5-6 x 10^9/L)	1.19	1.4	N/A

Figure 2. Table of the averages of abnormal labs (defined as out of reference range) based on whether a CRE occurred.

peaks at weeks 2 and 5. The average abnormal lab value resulting in a CRE for each test obtained can be seen in **Figure 2**. ALT (22%) and AST (27%) were the most commonly abnormal labs, and elevated ALT (103 vs 50.5, p=0.00087) and AST (53.5 vs 41.3, p=0.03) values were significantly higher in CREs.

DISCUSSION

This study was conducted to determine when within the first 90 days of methotrexate treatment CREs were most likely to occur and to define the specific values at which abnormal labs resulted in a CRE. We found that CREs occurred most frequently during week 11 with minor peaks at weeks 2 and 5. It is unclear why a major spike occurred at week 11; this could be a dose-dependent side effect that manifests after a cumulative methotrexate burden. The CREs occurring during week 11 may decrease future methotrexate burden, decreasing the likelihood of CREs in future weeks.

The values found for each lab in Figure 2 can be used to illustrate the level of tolerance that providers had for determining how far an abnormal laboratory test may deviate from the reference range before changing management. We found that ALT and AST values were significantly higher in patients with a CRE, suggesting that providers had a higher tolerance for abnormal values. This may be due to the limited specificity of elevated aminotransferases, leading to hesitancy to change management for moderately elevated values.

Methotrexate requires laboratory monitoring of blood counts, renal function, and liver function. However, current monitoring guidelines for dermatological patients on methotrexate are variable and highly provider- and institution-dependent, particularly within the first 90 days of therapy.[3] *Comprehensive Dermatologic Drug Therapy* recommends a CBC and LFTs every 1-2 weeks for the first 2-4 weeks and after dose escalations, with a gradual decrease to every 3-4 months long-term.[4] Rheumatologic guidelines governing methotrexate blood monitoring are generally less stringent. A 2018 study determined that strict monitoring by dermatologists led to more abnormal findings and reduced drug survival, with no difference in serious adverse events compared to rheumatology patients.[5]

A 2021 study determined that methotrexate was uncommonly discontinued for blood test abnormalities after the first year of prescription.[6] However, similar studies have not been conducted examining the first 90 days of treatment. Our study suggests that CREs for methotrexate use are uncommon (<5% of lab draws resulted in a CRE) within the first 13 weeks of methotrexate initiation, except during week 11.

Our research suggests that laboratory test frequency can be reduced during the first few months of methotrexate initiation. In patients without baseline hematologic, renal, or liver abnormalities, our data suggest that optimal timing of lab draws may be around weeks 2-5 and 11-12. Figure 2 can assist providers in determining if a CRE may be likely to occur depending on the amplitude of the laboratory value's deviation from reference ranges. However, without a consensus in laboratory monitoring guidelines, further research is warranted to determine the optimal timing and frequency of methotrexate laboratory draws. Additionally, we are limited by our inability to predict if an adverse outcome would have occurred without a change in drug management. Other limitations include the retrospective nature of study, possible inaccuracies in medical documentation,

generalizability of the study given the moderate sample size, and that all records were obtained at a single medical center.

In summary, we found that 1) abnormal labs most frequently led to a CRE at week 11 of monitoring, 2) ALT and AST were the most frequently abnormal labs, and 3) abnormal ALT and AST values were significantly higher in patients with CREs. Despite its limitations, this study provides valuable insight into an understudied dermatologic topic and hopefully will inform clinicians regarding methotrexate laboratory monitoring and spur further investigation.

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