Official Title

Comprehensive Assessment of Risk for Liver Fibrosis in Long-term Methotrexate Therapy (METOHEP)

Brief Title:

Liver Fibrosis Risk with Methotrexate Exposure

Acronym:

METOHEP

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Document Date:

4 November 2026

Keywords:

Liver fibrosis, Methotrexate, Toxicology, Rheumatoid arthritis, Psoriatic arthritis

Project Summary

Methotrexate (MTX) is widely used as an effective therapeutic option for various rheumatological diseases. However, approximately one-third of patients discontinue MTX due to hepatic adverse effects. An alternative therapy is subsequently selected, where biologic drugs have emerged as the preferred choice. Nevertheless, liver and systemic side effects remain, alongside the imminent risk of immunogenicity, which can occur at any point during treatment. Furthermore, the annual cost of MTX is lower than that of alternative therapies, amounting to approximately one-third of the cost of biologics.

In this proposal, we aim to identify the factors that may underlie the development of fibrosis in patients undergoing MTX treatment, and to determine whether this risk is exaggerated and can be explained by other contributing factors, such as obesity, concomitant medication, alcohol consumption, and other metabolic factors. We will include a retrospective cohort of patients who have been on MTX for more than 6 months,

The greatest potential benefit of this study is the attempt to challenge the widely accepted practice of discontinuing MTX due to fear of ongoing liver fibrosis. This could reduce the need for serial blood sampling, lower therapy costs, and correctly identify the underlying causes of liver fibrosis (obesity, excessive alcohol consumption, etc.) to allocate resources toward combating these specific risk factors—which will continue to damage the liver if left untreated, regardless of the choice of pharmacological therapy.

Project description

Background

Methotrexate (MTX) is a folic acid antagonist indicated for the treatment of a variety of conditions. However, MTX is presumed to damage the liver, which leads to drug discontinuation in > 10% of patients.

The mechanisms by which MTX damages the liver are not fully understood, but it is thought to involve a combination of factors, including:

Inflammation: MTX can cause inflammation in the liver, which can lead to the formation of fibrous tissue and scarring of the liver over time.

Oxidative stress: MTX can generate free radicals, which can cause damage to liver cells and contribute to the development of liver injury.

Impaired bile flow: MTX can interfere with the normal flow of bile from the liver, which can

lead to the buildup of bile acids and other toxins in the liver and contribute to liver damage. Impaired drug metabolism: MTX can cause changes in the activity of liver enzymes that are involved in the metabolism of drugs, which can lead to the accumulation of toxic levels of other drugs in the body.

Aims

The aim of this proposal is to determine whether liver fibrosis in patients treated with MTX is due to inherent properties of the drug, or if other factors, such as lifestyle, overweight and excessive alcohol consumption are the major contributing factor to liver enzyme elevation and fibrosis development.

Clinical question

To focus on identifying risk factors and developing methods for early detection and prevention of MTX liver toxicity. We will look at the impact of concurrent medications and lifestyle factors such as overweight and alcohol consumption. We will explore the usability of non-invasive imaging techniques and biomarkers to improve the monitoring of liver function in patients taking MTX.

Methods

Data analysis

1. Collect retrospective data from patients diagnosed with rheumatoid arthritis or psoriatic arthritis at the Department of rheumatology at Sahlgrenska University Hospital, Göteborg Sweden who have had and are currently on treatment with MTX > 6 months.

2. Assess the factors associated with liver fibrosis (lifestyle, metabolic profile, other medication history, alcohol consumption) in all included patients

3. Calculate indirect markers of liver fibrosis such as:

• AST to platelet ratio index - APRI, calculated using the AST elevation (which is the AST level divided by the upper limit of normal [ULN] for the lab) and the platelet count per mm3 divided by 1000.

• FIB-4 index which combines biochemical values (platelet count, ALT, and AST) and age.

4. Imaging examinations - elastography which estimates liver stiffness by applying mechanical waves and measuring their propagation speed through tissue using imaging. We will use transient elastography [TE] and acoustic radiation force impulse [ARFI] imaging.

Proposed statistical methods

1. Descriptive statistics for demographics and clinical data for continuous measurements, with either mean or median values +/- standard deviation or interquartile deviation depending on data distribution.
2. Comparison of clinical characteristics using relevant statistical methods depending on the available variables (ex. Fischer's exact test or T-test)
3. Spearman's rank correlation for the assessment of correlation between various fibrosis markers and elastography findings.
4. Logistic regression analysis (univariable and multivariable where indicated) to assess the relationship between MTX duration of therapy and cumulative dose and fibrosis development.
5. Other analyses where indicated.