

Serum Alpha Glutathione-S-Transferase

Maxwell, P.R.⁽¹⁾, Shaw M⁽²⁾, Mendonca, C.⁽³⁾ & Burden R., D.⁽³⁾. Department of Biochemistry

Abstract

ALPHA GLUTATHIONE S-TRANSFERASE AS A NOVEL BIOMARKER FOR MONITORING CHRONIC METHOTREXATE HEPATOTOXICITY

Maxwell¹, P-R. Burden³, R. and Shaw², M. ¹Glasgow Hospitals, Scotland and ²Biotrin International, Dublin, Ireland.

Methotrexate is a commonly used drug for treating severe psoriasis and other severe immunological diseases. It is a known hepatotoxin and it is recommended that liver function be monitored in patients and that liver biopsies are performed on patients after they have received fixed cumulative doses of 1-1.5g of the drug.

Improved monitoring of liver status could reduce the need for routine biopsies, saving costs and reducing patient morbidity, while identifying those most at risk.

Alpha glutathione S-transferase (α GST) is a more sensitive indicator of acute hepatocyte injury than transaminases, but it has not previously been studied as an indicator of chronic toxicity.

44 subjects receiving low dose methotrexate for psoriasis were monitored using α GST, ALT, AST, GGT, ALP and serum albumin. Only 5% of patients showed elevated ALT levels, but α GST levels were above normal in 25%.

In the immediate period after a dose of methotrexate (24-48 hours), AST and α GST were elevated but α GST was increased to a greater degree (over three fold compared with ~2 fold for AST). Other liver biomarkers were not significantly changed.

α GST is more often increased and to a greater degree than other biomarkers in subjects receiving chronic methotrexate therapy. Since subjects with normal transaminases would not normally be biopsied, α GST has the potential to identify those most at risk of hepatic injury.

Introduction

Methotrexate (MTX) is the main treatment available for severe psoriasis⁽¹⁾, however MTX induced hepatotoxicity may lead to fibrosis and cirrhosis⁽²⁾.

Current guidelines recommend a liver biopsy after a cumulative MTX dose of 1.5g or after the finding of consecutively abnormal liver function test (LFT) results⁽³⁾.

Due to the long-term nature of MTX therapy for psoriasis some patients may require serial biopsies.

Serum transaminase levels (AST and ALT) correlate poorly with hepatic histology and this finding has led to a search for other non-invasive biomarkers of hepatic damage in this patient group.

Alpha glutathione-S-transferase (α GST) is found in higher concentrations (5% of soluble cytoplasmic protein) and is more evenly distributed throughout the liver lobules than transaminases which exhibit a predominantly periportal distribution⁽⁴⁾.

Many studies have shown α GST to be a more sensitive indicator of acute hepatocyte injury than transaminases but few studies have been performed on chronic hepatotoxicity.

transferase as a Biomarker of Methotrexate

biochemistry, Stobhill Hospital, Glasgow, UK⁽¹⁾, Biotrin International, Dublin, Ireland

Aim

- To compare serum α GST with standard LFTs as biomarkers of liver injury in psoriasis patients receiving once weekly low dose MTX.

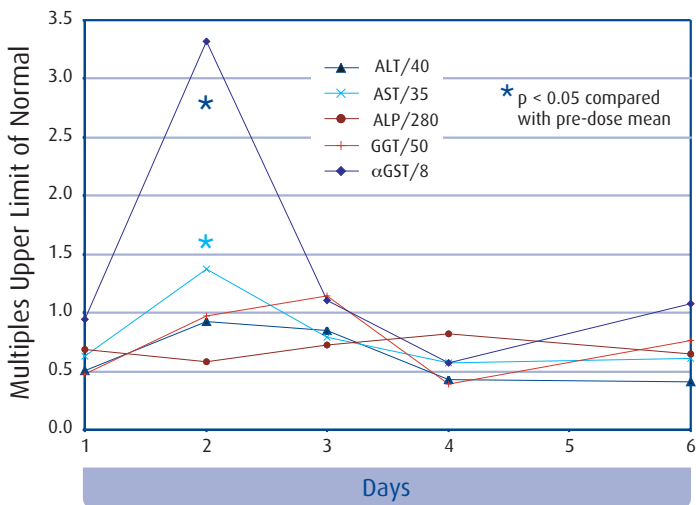
Patients & Methods

- CONTROLS: n = 20 (10 males : 10 females), age range 49:7 (mean : SD).
- PSORIATIC SUBJECTS: n = 44 (18 males : 26 females), age range 56:14 (mean : SD) .
- LFT PROFILE: Total protein, albumin, alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), aspartate transferase (AST) and alanine transferase (ALT) were measured by standard methodology on the Bayer ADVIA 1650 (Bayer, Tarrytown, NY, USA).
- Patients received between 5 –20 mg MTX /week.
- Serum α GST was measured using the Biotrin HEPKIT™-Alpha GST EIA (Biotrin International, Dublin, Ireland).

Results

- LFT and α GST results in controls and patients are shown in table 1 and figure 1.
- No differences between MTX and control subject groups were observed with regard to total protein, albumin, ALP, AST and ALT.
- Plasma GGT and α GST were, however, found to be significantly different ($p < 0.05$) between groups.
- In the patient group as a whole, no elevations in AST above the reference range were found, while for ALT only 2/44 patients (5%) had a level above the reference range. However, 11/44 (25%) had an α GST value above the reference range.
- In relation to weekly dose and cumulative MTX dose no linear correlation was found between any plasma index of hepatic function or integrity (data not shown).

Figure 1. Liver Biomarkers following MTX Dose



Methotrexate Induced Hepatotoxicity

Land⁽²⁾ & Department of Dermatology, Western Infirmary, Glasgow, UK⁽³⁾.

Table 1. Plasma Indices of Liver Function in Controls and Patients with Psoriasis. (Mean \pm 1SD).

Analyte	Control group	Patient group	Significance
Protein (g/L)	68 \pm 3	68 \pm 4	NS
Albumin (g/L)	41 \pm 3	43 \pm 3	NS
AST (U/L)	24 \pm 4	23 \pm 10	NS
ALT (U/L)	20 \pm 4	18 \pm 12	NS
ALP (U/L)	178 \pm 24	191 \pm 54	NS
GGT (U/L)	23 \pm 7	36 \pm 27	p<0.05
α GST (μ g/L)	3.6 \pm 1.0	9.0 \pm 7	p<0.01

Discussion

- Plasma α GST was elevated more often, and to a greater degree, than standard LFTs in subjects receiving chronic MTX therapy.
- As with components of the standard LFT profile, sampling time in relation to dosing is important.
- α GST showed the transient acute toxicity following a dose of MTX more clearly than standard LFTs.
- In the 24-48 hour period post dosing, both AST and α GST were found to be significantly elevated compared with pre-dose levels with α GST being elevated over three fold compared to about two fold for AST.

Conclusion

- α GST may be a more sensitive biomarker of liver injury in patients receiving MTX therapy.
- α GST has the potential to be an important additional biomarker of hepatic damage in patients receiving once weekly low dose MTX for severe psoriasis.
- Subjects with elevated plasma α GST, but normal transaminases, may be at increased risk of liver injury. Further clinical trials are needed to confirm this.

References

1. Roenigk, H.H. Jr., Auerbach, R., *et al.* Methotrexate guidelines - revised. J. Am. Acad. Dermatol. 1982; 6: 145-155.
2. Zachariae, H., Kragballe, K., *et al.* Methotrexate induced liver cirrhosis: studies including serial liver biopsies during continued treatment. Br. J. Dermatol. 1980; 102: 407-412.
3. Roenigk, H.H. Jr., Auerbach, R., *et al.* Methotrexate in psoriasis: revised guidelines. J. Am. Acad. Dermatol. 1988; 19: 145-146.
4. Beckett, G.J., Hayes, J.D.. Glutathione-S-transferases: Biomedical applications. Adv. Clin. Chem. 1993; 30: 281-380.

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