FoxP3-Expressing T Regulatory Cells (T-regs) Increase with the Severity of Active Disease in Chronic Hepatitis C

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Abstract

Background: The hepatitis C virus (HCV) leads to chronic disease in 80% of those infected and is associated with a chronic inflammatory response that is mediated by both cytokine producing ($CD4^+$) and cytotoxic T cells ($CD8^+$). FoxP3-expressing, $CD4^+$, $CD25^+$ T cells (T-regs) are a subset of T lymphocytes that inhibit immune responsiveness and, thereby, control immunological reactions. Whether $FoxP3^+$ T regulatory cell-mediated suppression is a factor in HCV persistence and/or the course of chronic liver injury has not been defined. In order to assess the association between these T regulatory cells and the severity of chronic hepatitis C, we evaluated liver biopsies for the density of FoxP3-expressing cells in relation to the degree of inflammation.

Design: Forty liver biopsies from patients with chronic hepatitis C were obtained from the archives of the Department of Surgical Pathology of Thomas Jefferson University Hospital. The biopsies were selected to be equally divided between those with mild and moderate-severe necroinflammatory activity based on a modified histological activity index (HAI) after Ishak et al.(J Hepatol 22:696, 1995). The biopsies were stained for FoxP3 (eBioscience Cat #14-4777-82). A representative area of portal inflammation was photographed at 400X, and the percentage of FoxP3+ cells relative to the total number of lymphocytes was calculated.

Result: The 20 cases of mild chronic hepatitis C had a mean necroinflammatory (HAI) score of 2.7 ± sd 1.1, whereas the moderate to severe cases had a mean HAI score of 7.6 ± sd 0.7 ($p< 0.001$, student t-test). The number of lymphocytes in a 400X field was greater in the moderate-severe cases than in the mild cases (412 ± sd 92 versus 182 ± sd 102; $p<0.001$, student t-test). The mean percentage of $FoxP3^+$ T cells among the mild cases was 7.4 ± sd 3.3. By contrast, the mean percentage of $FoxP3^+$ T cells among the moderate-severe cases was 14.2 ± 4.2 sd ($p< 0.001$, student t-test).

Conclusion: In chronic hepatitis C, $FoxP3^+$ T regulatory cells increased with greater inflammation that reflected, in turn, more severe liver disease. Thus, the density of T-regs reflected the activity of the chronic hepatitis. Such a conclusion does not support the hypothesis that greater activity in chronic hepatitis C is related to a reduced level of regulatory control by $FoxP3^+$ T cells (T-regs).

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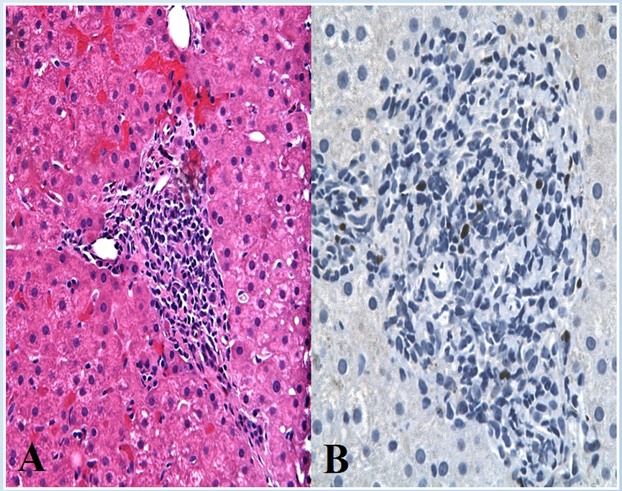

Figure 1 (A-B). Expression of FoxP3+ T-regulatory cells in chronic hepatitis C with mild activity (1A-hematoxylin-eosin, original magnification x 200; 1B-immunostain, original magnification x 400).

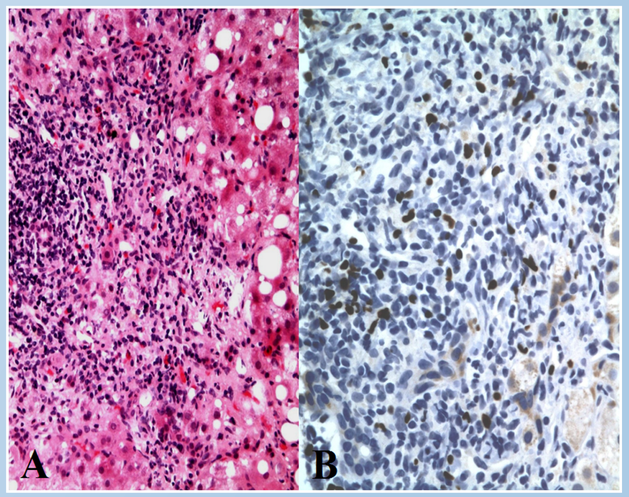

Figure 2 (A-B). Expression of $FoxP3^+$ T-regulatory cells in chronic hepatitis C with severe activity (1A-hematoxylin-eosin, original magnification x 200; 1B-immunostain, original magnification x 400).

	Severe Activity Average	Mild Activity Average
Necroinflammatory Score (Modified HAI Grading)	7.6	2.7
# of lymphocytes per HPF	412	182
% of FoxP3+ lymphocytes per HPF	14.20%	7.40%
For each measurement p<0.001 (student t-test)		

Conclusions

In chronic hepatitis C, $FoxP3^+$ T regulatory cells increased with greater inflammation that reflected, in turn, more severe liver disease. Thus, the density of T-regs reflected the activity of the chronic hepatitis. Such a conclusion does not support the hypothesis that greater activity in chronic hepatitis C is related to a reduced level of regulatory control by $FoxP3^+$ T cells (T-regs).