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## Alcoholic hepatitis: The pivotal role of Kupffer cells

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### Abstract

Kupffer cells play a central role in the pathogenesis of alcoholic hepatitis (AH). It is believed that alcohol increases the gut permeability that results in raised levels of serum endotoxins containing lipopolysaccharides (LPS). LPS binds to LPS-binding proteins and presents it to a membrane glycoprotein called CD14, which then activates Kupffer cells *via* a receptor called toll-like receptor 4. This endotoxin mediated activation of Kupffer cells plays an important role in the inflammatory process resulting in alcoholic hepatitis. There is no effective treatment for AH, although notable progress has been made over the last decade in understanding the underlying mechanism of alcoholic hepatitis. We specifically review the current research on the role of Kupffer cells in the pathogenesis of AH and the treatment strategies. We suggest that the imbalance between the pro-inflammatory and the anti-inflammatory process as well as the increased production of reactive oxygen species eventually lead to hepatocyte injury, the final event of alcoholic hepatitis.

**Key words:** Alcoholic liver disease; Alcoholic hepatitis; Macrophages; Kupffer cells

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**Core tip:** In this editorial we provide critical comments on the pivotal role of Kupffer cells on the development of alcoholic hepatitis with a focus on the pro-inflammatory as well as the anti-inflammatory pathways. We propose that the anti-inflammatory pathway should be further explored as a potential alternative for novel treatment strategies. This editorial is significant as it provides a platform for the future basic and clinical

research in elucidating the pathogenesis and developing the management strategies of this common clinical pathology - alcoholic hepatitis.

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## INTRODUCTION

Alcoholic hepatitis (AH) is defined as an acute hepatic inflammatory response to excess alcohol ingestion. It is estimated that 56809 hospital admissions in 2007 in the United States had a primary diagnosis of AH, 0.71% of all admissions<sup>[1]</sup>. In addition, hospitalization for AH is a leading cause of healthcare utilization<sup>[1]</sup>. In spite of such high costs and mortality, there has been little progress in the treatment strategies over the past 20 years. Histologically, alcoholic hepatitis is characterized by hepatocellular necrosis and immune cell infiltration around damaged hepatocytes<sup>[2]</sup>. This inflammatory and immune response leads to further hepatic injury and acute liver failure. Thus understanding this inflammatory cascade is vital to understanding alcoholic hepatitis and developing a treatment strategy. Currently there are only two pharmacologic treatments of AH: Corticosteroids and pentoxifylline. However these treatments are limited in their effectiveness and severe cases of AH still carry a short term mortality of 30%-50%<sup>[3]</sup>. Hepatic macrophages, called Kupffer cells, have been found to play a central role in hepatic inflammation<sup>[4]</sup>. Therefore, we will focus on providing a concise review of the role of Kupffer cells in AH, current treatments to disrupt this inflammatory pathway and potential basic and clinical research directions.

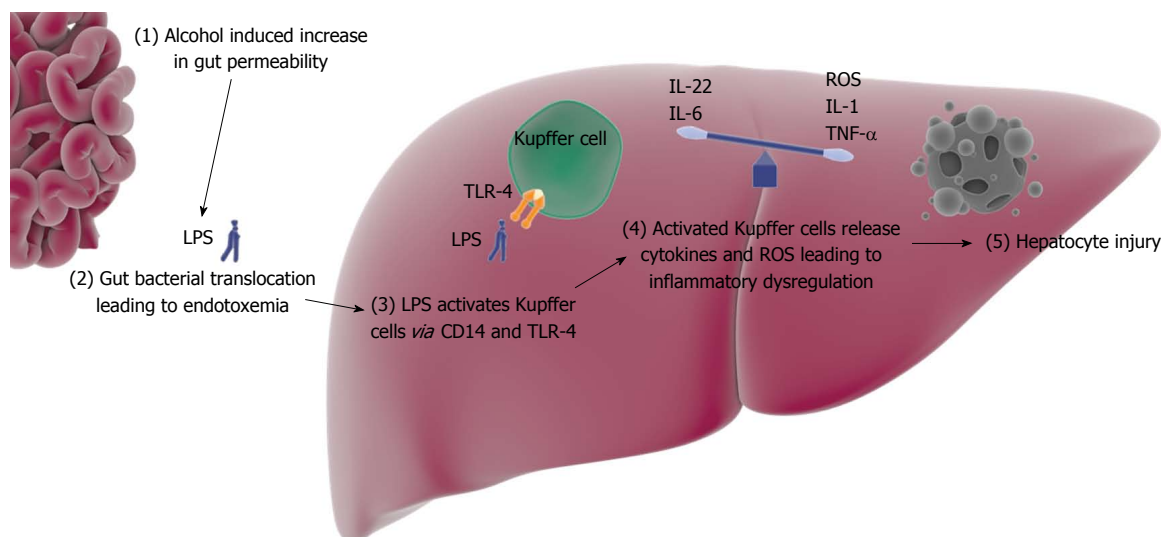
## OVERVIEW OF THE PHYSIOLOGIC FUNCTION OF KUPFFER CELLS

Kupffer cells are macrophages found in the liver. They were first identified by Kupffer<sup>[5]</sup> in 1876. Monocytes in the blood stream migrate into the liver and differentiate into Kupffer cells<sup>[6]</sup>. Kupffer cells makeup about 15% of all cells in the liver and comprise 50% of the total population of macrophages in the body<sup>[7]</sup>. They function to clear foreign matter from the portal circulation and in animal models have been shown to clear about 80%-90% of all particulate injected<sup>[8]</sup>. The particulate include immune complexes, bacterial components, endotoxins and collagen fragments. Kupffer cells can kill ingested organisms using oxygen dependent and independent mechanisms<sup>[9]</sup>. Studies in Kupffer cell depleted mice have shown that Kupffer cells play a critical role in neutrophil recruitment and granulomatous

formation in the liver<sup>[10]</sup>. Kupffer cells are activated by endotoxins (Figure 1). Endotoxins are composed of the lipopolysaccharides (LPS) component of Gram-negative bacterial cell walls. LPS-binding proteins (LBPs), produced by hepatocytes, bind and present LPS to CD14, a membrane glycoprotein<sup>[9]</sup>. CD14 in turn activates Kupffer cells *via* a membrane complex that includes a pathogen recognition receptor called toll-like receptor 4 (TLR-4). Activated Kupffer cells release interleukin (IL)-1B, tumor necrosis factor (TNF)- $\alpha$ , IL-6, IL-8, macrophage chemotactic protein-1 and regulated normal T cell expressed and secreted. These cytokines, mainly TNF- $\alpha$ , then bind to hepatocyte receptors leading to tissue damage *via* oxidative stress and apoptosis<sup>[11]</sup>.

## ACTIVATION OF IMMUNE RESPONSE IN ALCOHOLIC HEPATITIS

Gut bacterial translocation likely plays a key role in AH. In a healthy individual, only a small quotient of gut bacterial endotoxin gets translocated into the portal blood. Alcohol ingestion has been shown to increase this endotoxin translocation<sup>[12]</sup>. Alteration of gut microflora and increased gut permeability are the driving forces behind this process. Experimentally induced bacterial overgrowth in rats has been shown to lead to increased bacterial translocation and subsequent liver injury<sup>[13]</sup>. Furthermore, evidence suggests that alcohol can alter gut microflora<sup>[14]</sup>. Jejunal aspirates of chronic alcohol abuse patients have shown increased aerobic and anaerobic bacteria<sup>[15,16]</sup>. The pathophysiology of bacterial overgrowth in chronic alcoholic patients is not clearly identified. Possible etiologies include impaired bile flow, reduced gastrointestinal motility and increased gastric pH<sup>[14,17-19]</sup>. In addition to bacterial overgrowth, alcohol can lead to intestinal dysbiosis. Animal studies have shown an increased predominance of Gram-negative bacteria in alcohol fed subjects<sup>[20,21]</sup>. Mice with antibiotic induced eradication of gut flora had decreased alcohol induced liver injury as compared to mice with intact gut flora when exposed to ethanol<sup>[22]</sup>. Similar results were found in mice that were fed with lactobacillus<sup>[23]</sup>. Intestinal decontamination with rifaximin has also shown increased liver hemodynamics and decreased incidence of hepatic encephalopathy in patients with alcoholic liver disease (ALD)<sup>[24,25]</sup>. The second component of alcohol induced endotoxemia is increased gut permeability. Alcohol is metabolized into acetaldehyde, which has been shown to open tight junctions and increase gut epithelium permeability<sup>[26,27]</sup>. Several studies have suggested the association between endotoxins and alcoholic liver injury. It was found that endotoxin levels in mice directly correlated with the severity of alcoholic liver injury<sup>[28]</sup>. Rats that had LPS administered in addition to alcohol were also shown to have worse liver injury than those exposed to ethanol alone<sup>[29]</sup>. In humans, endotoxin levels have been shown to be measurably higher in acute and chronic alcohol use<sup>[30]</sup>.



**Figure 1 Central mediating role of Kupffer cells in alcoholic hepatitis.** The dysregulation between the pro-inflammatory and the anti-inflammatory cytokines eventually leads to hepatocyte injury. Image components obtained from somersault 1824 online image library (<http://www.somersault1824.com/>). LPS: Lipopolysaccharides; TLR-4: Toll-like receptor 4; IL: Interleukin; TNF: Tumor necrosis factor; ROS: Reactive oxygen species.

## IMPORTANCE OF KUPFFER CELLS IN ALCOHOLIC HEPATITIS

Several lines of evidence suggest that Kupffer cells play an important role as inflammatory mediators in the setting of alcoholic hepatitis. TLR-4 defective rats exposed to ethanol were shown to have markedly less steatosis, inflammation, and necrosis as compared to wild-type rats<sup>[31]</sup>. Furthermore ethanol increased TNF- $\alpha$  in wild-type rats but failed to do so in the TLR-4 mutant rats<sup>[31]</sup>. In LBP and CD14 knockout mice, alcohol induced liver injury was also significantly reduced<sup>[31-33]</sup>. Mice in whom Kupffer cells were chemically destroyed had no alcohol induced liver injury<sup>[34]</sup>. Activated human Kupffer cells express CD163, a hemoglobin-haptoglobin scavenger surface receptor<sup>[35]</sup>. Although the function of CD163 is unknown, it has been used as a marker for macrophage activation. Studies have shown that CD163 is in fact not only elevated in ALD, but that the plasma concentration of CD163 also predicts mortality in acute liver failure<sup>[36]</sup>. In addition CD163 has been shown to be a predictor of clinical decompensation in the setting of liver cirrhosis, an independent prognostic indicator for variceal bleeds and a marker of portal hypertension<sup>[37-39]</sup>. It is important to note that a recent study comparing levels of CD163 in AH, chronic cirrhosis and healthy patients found that CD163 concentrations were 30% higher in AH patients than in chronic cirrhotic patients and 10 times higher as compared to healthy individuals<sup>[40]</sup>. Therefore, CD163 could serve as a diagnostic marker of alcoholic hepatitis as well as a potential prognosticator for patients with alcoholic hepatitis.

Kupffer cell-mediated products have been extensively studied to further characterize their association in AH. TNF- $\alpha$  has been identified as a key mediator in AH. Serum TNF- $\alpha$  have been found to correlate with endo-

toxemia and development of inflammation and fibrosis in patients with AH. It can even be used as a biomarker for fibrosis<sup>[41,42]</sup>. Studies have confirmed that monocytes from patients with alcoholic hepatitis had greater levels of TNF- $\alpha$  than healthy subjects<sup>[43]</sup>. Furthermore, analysis of liver biopsies in patients with AH have shown increased staining for TNF- $\alpha$ , IL-1 and IL-6<sup>[44]</sup>. Kupffer cells can also contribute to liver injury *via* oxidant stress. Kupffer cells in animals fed with alcohol produce free radicals. This is further supported by studies showing nicotinamide adenine dinucleotide phosphate oxidase knocked out mice demonstrated to have decreased liver necrosis and inflammation in addition to decreased nuclear factor-kappa B and TNF- $\alpha$ <sup>[45]</sup>.

In addition to the resident Kupffer cell-mediated hepatic injury, recruited macrophages have also been shown to play a part in liver injury<sup>[46]</sup>. Murine models have shown that there is an increased accumulation of infiltrating monocytes in the setting of liver injury<sup>[47]</sup>. Recruitment of these monocytes is highly dependent on the chemokines CCL1 and CCL2. Of note, one of the major sources of CCL2 is hepatic stellate cells, which in turn are activated by the TLR-4 ligands. Mice lacking CCL2 have been shown to incur less liver injury<sup>[48]</sup>. Furthermore mice lacking CCR8, a receptor for CCL1, were also shown to be more protected from liver injury<sup>[49]</sup>. Infiltrating monocytes have been divided into two groups depending on surface protein expression, Ly6C<sup>hi</sup> and Ly6C<sup>low</sup>. Ly6C<sup>hi</sup> monocytes exhibit a pro-inflammatory phenotype while Ly6C<sup>low</sup> monocytes exhibit an anti-inflammatory phenotype. Mice fed with ethanol had a shift towards more Ly6C<sup>hi</sup> monocytes, resulting in significantly increased liver injury<sup>[50]</sup>. There is still much to be learned about the role and function of infiltrating monocytes in liver injury.

Kupffer cells have been shown to play central roles in other causes of liver injury such as nonalcoholic

**Table 1** Randomized controlled trials evaluating the treatment of alcoholic hepatitis

| Study                                   | Topic                                | Methods   | Findings                            |
|---|--------------------------------------|---|-------------------------------------|
| Prednisolone or pentoxifylline          |                                      |   |                                     |
| Theodossi <i>et al</i> <sup>[99]</sup>  | PRED <i>vs</i> placebo               | Randomized control                              | No difference in mortality          |
| Ramond <i>et al</i> <sup>[100]</sup>    | PRED <i>vs</i> placebo               | Double-blinded, randomized control              | Improved mortality with PRED        |
| Akriviadis <i>et al</i> <sup>[69]</sup> | PTX <i>vs</i> placebo                | Double-blinded, randomized control              | Improved mortality with PTX         |
| Sidhu <i>et al</i> <sup>[101]</sup>     | PTX <i>vs</i> placebo                | Randomized control                              | Improved mortality with PTX         |
| De <i>et al</i> <sup>[102]</sup>        | PTX <i>vs</i> PRED                   | Double-blinded, randomized control              | Reduced mortality with PTX          |
| Park <i>et al</i> <sup>[103]</sup>      | PTX <i>vs</i> PRED                   | Randomized control                              | Reduced mortality with PRED         |
| Mathurin <i>et al</i> <sup>[104]</sup>  | PRED <i>vs</i> PRED + PTX            | Multicenter, double-blinded, randomized control | No difference in mortality          |
| De <i>et al</i> <sup>[105]</sup>        | PTX <i>vs</i> PTX + PRED             | Double-blinded, randomized control              | No difference in mortality          |
| Thursz <i>et al</i> <sup>[70]</sup>     | PTX <i>vs</i> PRED <i>vs</i> placebo | Multicenter, double-blinded, randomized control | No difference in mortality          |
| N-acetylcysteine                        |                                      |   |                                     |
| Moreno <i>et al</i> <sup>[106]</sup>    | NAC <i>vs</i> placebo                | Multicenter, single-blinded, randomized control | No difference in mortality          |
| Cytokine inhibitors                     |                                      |   |                                     |
| Naveau <i>et al</i> <sup>[72]</sup>     | Infliximab <i>vs</i> placebo         | Double-blinded, randomized control              | Increased mortality with infliximab |
| Boetticher <i>et al</i> <sup>[71]</sup> | Etanercept <i>vs</i> placebo         | Multicenter, single-blinded, randomized control | Increased mortality with etanercept |

PTX: Pentoxifylline; PRED: Prednisolone; NAC: N-acetylcysteine.

steatohepatitis (NASH) and viral hepatitis that are often also present in AH patients. Using a murine model of NASH, several studies have shown that sequential depletion of Kupffer cells reduced the incidence of steatosis<sup>[51-53]</sup>. Furthermore, targeted knockdown of TNF- $\alpha$  also decreased the incidence of NASH development<sup>[51,54]</sup>. Current understanding of the role of Kupffer cells in viral hepatitis is limited. Identification of a specific pathogenesis has been difficult due to similar characteristics of recruited macrophages and resident Kupffer cells. A recent study suggests that Kupffer cell interaction with hepatitis B surface antigen leads to pro-inflammatory cytokine production, which may contribute to liver pathology<sup>[55]</sup>. Studies have shown increased numbers of Kupffer cells during hepatitis C viral (HCV) infection<sup>[56]</sup>. Incubation of HCV E2 envelop protein with human liver cells resulted in Kupffer cell binding in a CD81-dependent manner<sup>[57]</sup>. In addition HCV core and NS3 stimulate human CD14<sup>+</sup> Kupffer cells and monocyte derived macrophages to produce IL-1 $\beta$ , IL-6 and TNF- $\alpha$ <sup>[58,59]</sup>. It is likely that Kupffer cell activation contributes to the progression of liver disease in viral hepatitis. Increased numbers of Kupffer cells have been found in regions of liver fibrosis in the setting of chronic viral hepatitis<sup>[60]</sup>. Viral hepatitis has also been shown to induce Kupffer cells to release cytotoxic molecules that kill not only infected hepatocytes but also non-infected cells<sup>[61,62]</sup>. It is likely that Kupffer cells are involved in the pathogenesis of many types of liver pathologies and it may be the case that their activation is multifactorial in patients with AH as well as other hepatic comorbidities.

## CURRENT TREATMENT OF ALCOHOLIC HEPATITIS

AH is an acute process and most patients will recover with nutritional support and abstinence from alcohol. However severe AH carries a high mortality rate: 35% at 28 d without effective treatment<sup>[63]</sup>. These high mor-

tality rates are predominantly due to a lack of effective treatment for severe AH. Multiple clinical trials for treatment of alcoholic hepatitis have been published (Table 1). The American Association for the Study of Liver Diseases (AASLD) guidelines for management of AH currently stratifies the management depending on severity. Low risk patients are managed conservatively with nutrition, supportive care and close monitoring. High-risk individuals, defined as those with a Maddrey's discriminant function greater than or equal to 32 or a model for end-stage liver disease score greater than or equal to 18, may benefit from pharmacological intervention with either prednisolone or pentoxifylline. Corticosteroids have been extensively studied with mixed results<sup>[63-67]</sup>. This is likely due to the fact that study design, severity of AH and exclusions criteria vary greatly between studies. One meta-analysis showed survival rates of 80% at 28 d with corticosteroids vs 66% in the control group in patients with severe AH<sup>[63]</sup>. Corticosteroids presumably improved outcomes by decreasing pro-inflammatory cytokines. Pentoxifylline is a nonselective phosphodiesterase inhibitor that increases intracellular concentration of adenosine 3', 5'-cyclic monophosphate, which in turn inhibits the expression of pro-inflammatory cytokines<sup>[68]</sup>. AASLD recommends pentoxifylline as an alternative to corticosteroids when the use of steroids is contraindicated or in the setting of early renal failure. According to one randomized, double-blinded, placebo controlled trial, patients treated with pentoxifylline had a survival benefit (24.5% mortality vs 46.1% in the placebo group)<sup>[69]</sup>. Although multiple clinical trials have shown some benefit of treatment with steroids or pentoxifylline, a recent well designed, multicenter, double-blinded, randomized trial found no statistically significant mortality benefit in treatment with either pentoxifylline or prednisolone<sup>[70]</sup>. The study involved 1053 patients who were randomized to four arms: A group that received a pentoxifylline-matched placebo and a prednisolone-matched placebo, a group that received prednisolone and a pentoxifylline-matched



placebo, a group that received pentoxifylline and a prednisolone-matched placebo, or a group that received both prednisolone and pentoxifylline. The prednisolone group was the only group associated with an initial reduction in 28-d mortality. However at 90 d and at 1 year there were no significant differences between the groups. There is no doubt that this well designed study certainly questions the currently established treatments of AH.

While cytokine inhibitors have great potential in theory, trials with both infliximab and etanercept have resulted in increased mortality, primarily due to infection<sup>[71,72]</sup>. Liver transplantation is another treatment option in ALD. Most transplant centers require at least 6-months of abstinence<sup>[73,74]</sup>. This allows for disease regression in patients with recent alcohol use, time for proper counseling and demonstrates patients' ability to abstain from alcohol. One meta-analysis comparing alcohol use in post-transplant patients showed no difference in the proportion of patients that used alcohol when comparing ALD to non-ALD patients, although ALD patients were more likely to drink excessively<sup>[75]</sup>. Risk of alcohol recurrence in ALD transplant patients continues to be an area of debate. In summary, treatment options for AH are limited with even the standard of care now being questioned, emphasizing the urgent need for effective and novel treatment strategies.

## FUTURE AREAS OF RESEARCH

Identification of new therapeutic targets has been hampered by a lack of appropriate animal models. Current animal models do not develop severe liver injury as humans do. One possible area of future investigations would be the modulation of the LPS pathway. A recent study evaluating the effects of milk osteopontin on gut permeability found that milk osteopontin preserved gut architecture and prevented inflammation in ethanol fed mice<sup>[76]</sup>. Milk osteopontin has also been shown to directly bind to LPS and prevent Kupffer cell activation thereby disrupting the subsequent pro-inflammatory cascade<sup>[77]</sup>. Another study used probiotics to alter gut flora and TLR4 antagonists, which have been proposed for treatment of ALD<sup>[78]</sup>.

Genetic factors leading to the predisposition for liver disease is another promising area of exploration in recent years. A number of studies have shown an association between variations in the *PNPLA3* gene and liver fat content as well as plasma aspartate aminotransferase<sup>[79-82]</sup>. Furthermore two groups have independently found associations between the *PNPLA3* single-nucleotide polymorphism rs738409 and ALD populations in Mexico and Germany<sup>[83,84]</sup>. During the last decade, a prominent area of research had been the inhibition of pro-inflammatory cytokines. However blocking TNF- $\alpha$  had led to unacceptable complications. More targeted inhibition using dexamethasone conjugates targeting the CD163 receptor on macrophages have shown some

success in rats<sup>[85,86]</sup>. Yet another unique way of managing inflammation in AH patients is apheresis. A recent case series and literature review of 35 cases concluded that leukocytapheresis and granulocytapheresis were effective in controlling leukocytosis as well as inflammatory cytokines<sup>[87]</sup>.

In contrast to pro-inflammatory cytokines, Kupffer cells also produce anti-inflammatory or hepato-protective cytokines, such as IL-6 and IL-22<sup>[88]</sup> (Figure 1). Activated Kupffer cells release IL-6, which then stimulates signal transducer and activator of transcription 3 (STAT3) leading to increased expression of genes that are anti-apoptotic, anti-oxidative, and promote mitochondrial DNA repair<sup>[89,90]</sup>. Studies have shown that IL-6 deficient mice are in fact more susceptible to hepatic steatosis, cellular apoptosis and mitochondrial DNA damage when exposed to ethanol<sup>[89-91]</sup>. Furthermore STAT3 knockout mice have been shown to have greater degree of hepatic steatosis as compared to wild-type mice<sup>[92]</sup>. Ethanol induced liver injury was alleviated by treatment with IL-6<sup>[93]</sup>. IL-22 is another hepato-protective cytokine that has been found to ameliorate hepatocellular damage in fatty liver as well as acute and chronic alcoholic liver injury<sup>[94-97]</sup>. It is believed that both IL-6 and IL-22 share the same pathway, STAT3 mediated hepatoprotection<sup>[96]</sup>.

Another potentially important observation relevant to alcoholic hepatitis is a recently reported finding that the administration of lactate reduced inflammation and organ injury in mice with an immune mediated hepatitis<sup>[98]</sup>. Lactate interacted with the specific receptor G protein-coupled receptor 81 (GPR 81) to reduce inflammation and injury. Further, lactate and GPR 81 prevented LPS-induced macrophage activation (Kupffer cells) suggesting that the beneficial effects were mediated by the effects of lactate on activated macrophages. These results suggest that hepatic injury due to macrophage activation may be treated by ligands including lactate that interact with GPR 81.

## CONCLUSION

AH is a major cause of morbidity and mortality worldwide. The underlying mechanisms are poorly understood, which has resulted in a lack of specific treatments. The absence of animal models further hampered the progress in elucidating the molecular mechanisms which may provide scientific evidence for designing more targeted treatment strategies. Given the inconsistent results of currently available treatment strategies, which mainly target the pro-inflammatory process, we speculate that it is also important to recognize the potential effort of targeting the anti-inflammatory pathway or targeting both the anti and the pro-inflammatory pathways simultaneously. With the recognition of the anti-inflammatory process mediated by Kupffer cells, it may be the prime time for a well-designed clinical trial to target the unique anti-inflammatory pathway. This may lead to the development of novel effective treatment strategies for

this common clinical entity.

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