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GUIDELINES FOR BASIC SCIENCE

Molecular targets in the treatment of alcoholic hepatitis

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Abstract

Alcohol related costs to health and society are high. One of the most serious complications of alcohol misuse to the individual is the development of alcoholic hepatitis (AH), a clinical syndrome of jaundice and progressive inflammatory liver injury in patients with a history of recent heavy alcohol use. It has a poor outcome and few existing successful therapies. The use of glucocorticoids in patients with severe AH is still controversial and there remains a group of patients with glucocorticoid-resistant disease. However, as our understanding of the pathogenesis of the condition improves there are opportunities to develop new targeted therapies with specific actions to control liver inflammation without having a detrimental effect on the immune system as a whole. In this article we review the molecular mechanisms of AH concentrating on the activation of the innate and adaptive immune response. We consider existing treatments including glucocorticoids, anti-tumor necrosis factor therapy and pentoxifylline and their limitations. Using our knowledge of the disease pathogenesis we discuss possible novel therapeutic approaches. New targets include pro-inflammatory cytokines such as interleukin (IL)-17, chemokines and their receptors (for example IL-8, CXCL9 and CXCR3) and augmentation of anti-inflammatory molecules such as IL-10 and IL-22. And there is also future potential to consider combination therapy to selectively modulate the immune response and gain control of disease.

Key words: Alcoholic hepatitis; Tumour necrosis factor-α; Pentoxifylline; Interleukins; Chemokine receptors

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INTRODUCTION

Alcohol related morbidity in developed countries is second only to tobacco use and is responsible for 2.5 million deaths globally each year[1]. It costs 1% of the GDP of middle to high income countries[2]. In the United Kingdom, deaths from alcohol related liver disease have increased by 36% between 2001 and 2008[3]. Alcoholic hepatitis (AH) is a clinical syndrome characterised by jaundice and progressive inflammatory liver injury in patients with a history of recent heavy alcohol misuse. Severe cases are associated with a high mortality of around 30%-50% at 28 d[4,5]. However, the pathogenesis of the

condition is incompletely understood and there is a lack of targeted therapy.

It is clear that alcohol acts both directly on the liver, causing cell death by toxic mediators, and *via* activation of the immune system. Over the past 2 decades considerable headway has been made into understanding the immune basis of the disease with studies on pro- and anti-inflammatory cytokines, cell trafficking to the liver and mechanisms of hepatocyte death. This work has been hampered by the absence of a suitable animal model of the disease and much of the relevant work has been inferred from other models of acute hepatic injury or through chronic ethanol feeding. Although these models share several important similarities with human AH, such as neutrophil accumulation in the hepatic ischaemia model or hepatocyte ballooning in the ethanol-fed rat model, they still have significant differences. Neither the acute hepatic ischaemia model nor the carbon tetrachloride model involves alcohol metabolism and alcohol related liver damage. The chronic ethanol feeding model does not mirror the acute phase of inflammation in AH and instead is more similar to alcoholic steatohepatitis[6]. Therefore, at present we must interpret results from these studies with caution and focus attention on studies on human tissue.

In this review, we consider the pathogenesis of AH, focussing on the contribution of immunity (Figure 1), and relate this to the use of targeted molecular therapies. We briefly discuss the evidence for anti- tumor necrosis factor-α (TNFα) therapies and pentoxifylline, both of which have been extensively studied in AH, but do not intend this to be a definitive systematic review. For further discussion on these 2 treatments we refer the readers to recent comprehensive reviews[7-9]. We have emphasised the molecules that we believe have the greatest future therapeutic potential.

PATHOGENESIS

Within the liver alcohol can be metabolised to acetaldehyde by three enzyme systems: alcohol dehydrogenase in the cytosol, the microsomal ethanol-oxidising system and peroxisomal catalase. These metabolic pathways lead to the production of reactive oxygen species and cause lipid peroxidation. There is a reduction in the hepatoprotective methyl donor S-adenosylmethionine and mitochondrial glutathione. Acetaldehyde forms adducts with proteins, lipids and DNA, impairing their function and promoting DNA damage (see Setshedi *et al*[10] for a detailed review on this subject). However, it is not only the direct toxic effect of alcohol on the liver that causes damage but also activation of the immune response.

Activation of the innate immune system

Alcohol is known to change the gut microbiota[11] and can increase numbers of both aerobic and anaerobic organisms[12]. In addition, metabolism of alcohol by gut bacteria results in production of acetaldehyde which has a direct effect on the gut epithelium, opening up tight junctions, increasing its permeability[13,14]. This allows the presentation of bacteria or microbial cellular components to cells of the innate immune system. These pathogen-associated molecular patterns are recognised by toll-like receptors (TLRs) which are expressed on a wide variety of immune and stromal cells, in particular on monocytes and macrophages. Gut-derived endotoxin [or lipopolysaccharide (LPS)] crosses into the portal venous system and activates TLR4 on $CD14^+$ cells. Higher levels of LPS have been demonstrated in the portal veins of patients with alcohol related cirrhosis compared to non-alcohol related cirrhosis controls[15]. *Via* adaptor molecules MyD88 and toll/interleukin (IL)-1 receptor domain-containing adaptor inducing interferon-β, the signalling pathway converges on a few transcription regulators [nuclear factor κB (NF-κB), activator protein 1 (AP-1) and interferon regulatory factors], which lead to a pro-inflammatory immune response. Signalling through TLR4 plays an important role in the development of alcohol related liver damage as evidenced by TLR-mutant mice which are resistant to alcohol and have lower levels of circulating TNFα despite having higher circulating LPS[16]. Modulation of the gut microbiota with pro- or antibiotics reduces circulating levels of LPS in mouse models[17,18]. Activation of TLR4 on macrophages and kupffer cells (liver resident macrophages) leads to secretion of pro-inflammatory cytokines such as IL-1, IL-6 and TNFα, which act on surrounding hepatocytes and stromal cells as well as activating the adaptive immune response.

Activation of the adaptive immune system

It is clear that T-lymphocytes play a role in the development of AH with increased levels of $CD4^+$ and $CD8^+$ T-lymphocytes found in liver biopsy material from patients with AH compared to healthy controls[19]. The liver has a unique dual blood supply with both portal venous and hepatic arterial blood draining into the hepatic sinusoids. Hepatic sinusoid endothelial cells (HSEC) are therefore exposed to large numbers of leukocytes and HSEC expression of adhesion molecules and chemokine receptors enables adherence of lymphocytes and transmigration into the hepatic parenchyma to the site of inflammation. Unlike other endothelial cells HSEC express low levels of selectins[20] but high levels of intercellular adhesion molecule-1 (ICAM-1), vascular adhesion protein-1 (VAP-1) and vascular cell adhesion molecule-1 (VCAM-1)[21]. Inhibition of ICAM-1 and VCAM-1 reduce lymphocyte adhesion in *in vitro* flow-based adhesion experiments[21].

Liver infiltrating lymphocytes express high levels of CXCR3 and migrate towards its ligands CXCL9 and CXCL10[22], which are produced by a variety of liver cells including hepatic stellate cells and activated myofibroblasts[23]. High levels of TNFα found in AH stimulate production of CXCL10 from hepatocytes and HSECs increasing T cell recruitment to the liver[24]. Data from

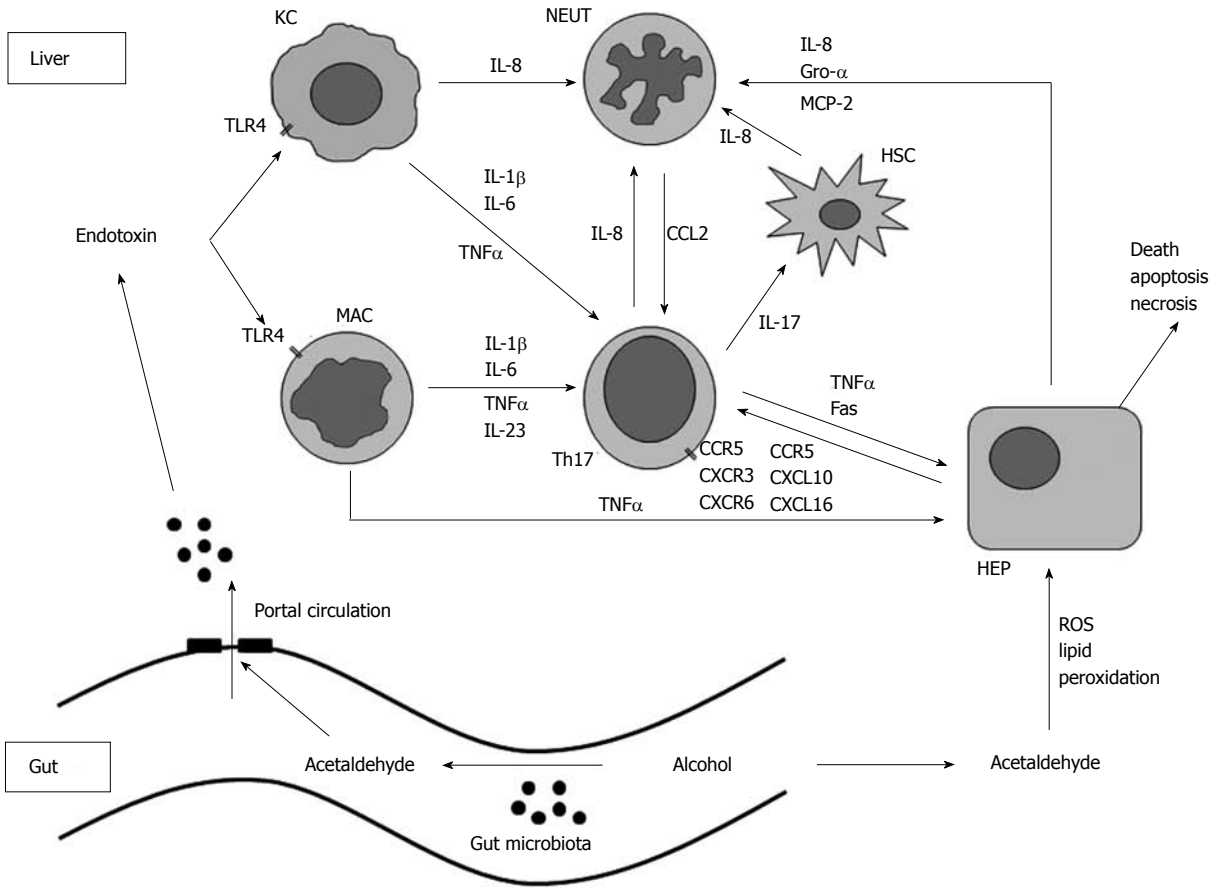

Figure 1 The effects of alcohol on the innate and adaptive immune system. Alcohol is metabolised by gut microbiota to acetaldehyde which has a direct effect on the epithelial tight junctions, making them more leaky. Endotoxin and other pathogen-associated molecular patterns enter the portal circulation and act *via* toll-like receptor (TLR) 4 receptors on kupffer cells (KCs) and macrophages (MAC), activating them to produce pro-inflammatory cytokines and chemokines, which act on hepatocytes, neutrophils (NEUT) and T cells. Both $CD4^+$ and $CD8^+$ T cells are recruited into the liver but there is a significant proportion of interleukin (IL)-17 secreting $CD4^+$ Th17 cells, which in turn activate stellate cells to produce IL-8. T cells also act directly on hepatocytes *via* the tumor necrosis factor (TNF) receptor 1 or Fas pathways leading to apoptosis. Alcohol also has a direct effect on hepatocytes (HEP) through metabolism by alcohol dehydrogenase, the microsomal ethanol-oxidising system and peroxisomal catalase to acetaldehyde, which damages cells by the formation of reactive oxygen species (ROS) and increased lipid peroxidation. HSC: Hepatic stellate cell; MCP: Monocyte chemotactic protein.

patients with chronic hepatitis C infection also demonstrate that liver infiltrating lymphocytes express high levels of chemokine receptor CXCR3 as well as others such as CCR5 and CXCR6[24,25].

Once T-lymphocytes have been recruited to the site of inflammation there is evidence that the $CD4^+$ subset mediates hepatocyte death. Adoptively transferred liver associated $CD4^+$ T cells from ethanol-fed rats demonstrated greater hepatocyte apoptosis in recipient rats compared to those transferred from non-ethanol-fed rats[26].

Hepatocyte death can occur by necrosis or apoptosis. Necrosis is characterised by ballooning and is clearly described in cases of AH. However, apoptosis has also been identified as an important mechanism of AH. There is greater hepatocyte apoptosis in the livers of patients with AH compared to controls[27] and the degree of apoptosis correlates with clinical measures of severity[28]. Apoptosis may be caused by direct cytotoxic T cell activation of the Fas apoptosis pathway, which in turn can induce IL-8, a neutrophil chemotaxin. Alternatively, TNFα binding to TNF-R1, a member of the death receptor family, can initiate apoptosis. As discussed above, TNFα is significantly elevated in severe AH suggesting it can mediate hepatocyte death by this mechanism as well as by direct toxic effects leading to necrosis.

Neutrophil recruitment

The degree of intrahepatic neutrophil infiltration correlates with severity of AH[29] although their exact role in the pathogenesis of the disease is less well understood. Data from animal models of other acute liver injury such as ischaemia suggest that neutrophils are activated by cytokines including TNFα, IL-1β and IL-17 and are recruited to the hepatic parenchyma by CXC chemokines such as Gro-α[29], IL-8 and monocyte chemoattractant protein 2[30]. CXC chemokines are particularly important for neutrophil infiltration in AH[31]. These neutrophils migrate into the parenchyma and cause hepatocyte necrosis by release of reactive oxygen species and proteases[32].

With this understanding of the molecular mechanisms of the pathogenesis of AH, we can more effectively target therapy.

Existing therapy for severe AH

Glucocorticoids: Glucocorticoid therapy was first demonstrated to be beneficial in the treatment of patients with severe AH in 1978[4]. Glucocorticoids are potent immunosuppressants which have wide ranging effects on a large number of cell types. Key among their actions is suppression of the pro-inflammatory transcription factors NF-κB and AP-1[33] resulting in lower levels of circulating TNFα and IL-8[34].

Glucocorticoid treatment has been evaluated in many clinical trials and debate continues whether they are beneficial with conflicting results of meta-analysis[35-37]. The largest placebo-controlled trial recruited a heterogeneous group of 90 patients (including those with moderate and severe disease as well as end stage alcoholic liver disease) and failed to show a survival benefit at 30 d[38]. Another trial recruiting only patients with histologically proven AH showed a survival benefit with glucocorticoid treatment at 2 mo[39] but no difference at long term follow-up at 2 years[40]. More recent meta-analysis of individual patient data demonstrated a survival benefit with glucocorticoid treatment in patients with severe AH[5]. However, they identify a proportion of glucocorticoid non-responders, with a significantly worse outcome, by applying the Lille model[41] at day 7 of treatment. This highlights the fact that as in other inflammatory diseases such as asthma and rheumatoid arthritis there is a proportion of patients resistant to steroid treatment[42]. In addition, the non-specific effect of glucocorticoids means that there is a risk of infective complications. Other therapeutic options are therefore essential.

Pentoxifylline: Pentoxifylline, a phosphodiesterase inhibitor, has a moderate effect on TNFα levels[43-45] although circulating TNFα levels in patients on active treatment did not show any difference from those on placebo in a randomised controlled trial[46]. The effects of pentoxifylline are likely to be less specific than inhibition of a single cytokine. In animal models of liver injury it has shown a reduction in pro-fibrogenic cytokines such as pro-collagen I and transforming growth factor beta 1[47]. Although the exact mechanism of action of pentoxifylline in AH is not clear several trials have shown a survival benefit, predominantly through a significant reduction in mortality due to hepatorenal syndrome[46,48]. However, a recent Cochrane systematic review was unable to draw firm conclusions about its beneficial effect due to probable bias in the design of a number of trials[49]. A large United Kingdom multi-centre randomised placebo-controlled trial of pentoxifylline, prednisolone or combination is currently underway, which hopes to provide a definitive answer as to whether these treatments are beneficial in patients with severe AH.

Anti-oxidant therapy: Oxidative stress plays an important role in the pathogenesis of AH (Dey *et al*[50]). In an attempt to reduce its toxic effects, several clinical trials of anti-oxidant agents have been undertaken either in combination with glucocorticoids or as a monotherapy. A recent randomized controlled trial (RCT) of 5 d of intravenous N-acetylcysteine (NAC) or placebo with 4 wk of glucocorticoids[51] demonstrated a reduction in mortality at 1 mo in the NAC arm but failed to reach significance at 2 mo and 6 mo (the primary outcome of the trial). A lower incidence of infections was noted in the NAC treated group.

A further RCT has been reported using an anti-oxidant cocktail (including NAC and vitamin E) with or without concomitant glucocorticoids, which failed to show an improvement in 6 mo survival[52]. A different anti-oxidant cocktail was tested against glucocorticoid therapy but a higher number of deaths at 30 d was reported in the anti-oxidant treatment arm[53]. Vitamin E versus placebo also failed to demonstrate any benefit in outcome[54].

Anti-TNFα therapy: Anti-TNF therapy with chimeric monoclonal antibody (infliximab) or fusion proteins (etanercept) have proved successful in other inflammatory conditions such as rheumatoid arthritis[55] and Crohn's disease[56]. With high levels of TNFα demonstrated in patients with severe AH[57] and since TNFα predicts short-[58] and long-term survival[59], it is an appropriate target for effective therapy.

In ethanol-fed rats treated with anti-TNF antibody, there was a significant improvement in hepatic inflammation, although serum levels of TNFα remained unchanged[60] supporting a role for this drug in human AH. An open label pilot study of a single dose of 5 mg/kg infliximab in combination with glucocorticoids found a significant reduction in Maddrey Discriminant Function[61]. An RCT of 3 infusions of infliximab 10 mg/kg or placebo at weeks 0, 2 and 4 in combination with prednisolone was stopped early due an excess of deaths in the active treatment group due to infection[62]. An RCT of etanercept also found that there was a significantly poorer outcome for patients on active treatment due to infection[63]. Lower doses of infliximab or less aggressive loading regimes may reduce the incidence of infection. Alternatively, combination therapy with an anti-inflammatory treatment such as recombinant IL-10 or IL-22 (see below) may boost the immune response to infections.

Alteration of the gut microbiota

Alcohol alters the gut microbiota and together with increased intestinal permeability there is activation of the innate immune system to produce an inflammatory response in AH. No clinical trial of probiotics has yet been reported in patients with AH. However, there is evidence that changing the bowel microbiota with probiotics in patients with alcohol related cirrhosis reduces the production of pro-inflammatory cytokines[64] and improves liver function tests in patients with alcoholic psychosis[65]. Further investigation is required to determine whether probiotic therapy is beneficial in AH. Alteration of the gut microbiota with non-absorbable antibiotics

such as rifaximin may also be beneficial and has recently been proven effective for the prevention of hepatic encephalopathy in patients with cirrhosis[66].

The treatments for AH discussed so far have wide-ranging effects on the immune system. These non-targeted therapies have failed to demonstrate a clear benefit in outcome. Both anti-TNFα therapy and glucocorticoids suppress the appropriate immune response to infection, resulting in a higher incidence of serious infections. Over the last decade the emphasis in treatment of inflammatory conditions has shifted to a more targeted approach to lessen the impact of inflammatory mediators, while reducing the systemic complications of treatment.

Future molecular targets

IL-10: IL-10 is a potent anti-inflammatory cytokine, suppressing the production of inflammatory cytokines (including TNFα) by T helper cells, monocytes and kupffer cells. IL-10 can also inhibit production of reactive oxygen species by neutrophils[67]. IL-10 is upregulated in surviving patients that had a response to glucocorticoid therapy[34]. This is consistent with studies of glucocorticoid effects on T cells in other inflammatory conditions such as asthma[68]. Therefore increasing the levels of IL-10 in patients with significant inflammation may prove to be a useful therapeutic target.

Unfortunately, treatment with recombinant human IL-10 (rhuIL-10) in patients with Crohn's disease has proved disappointing. Although well tolerated, it failed to induce clinical remission or response in patients with mild to moderately active Crohn's disease[69,70] and a recent systematic review suggested a lack of effect of rhuIL-10 in patients with Crohn's[71]. One study found that administration of rhuIL-10 lead to an increased capacity of leucocytes to produce interferon-gamma (IFNγ), a potent Th1 secreted pro-inflammatory cytokine[72], which may explain its lack of anti-inflammatory effect.

In the context of liver disease, rhuIL-10 has been trialled in chronic hepatitis C. Thirty patients with advanced fibrosis who failed treatment with antiviral therapy were treated with rhuIL-10 administered subcutaneously daily or 3 times weekly for 1 year[73]. There was a significant improvement in serum transaminase and a reduction in inflammation scores in 13 of 28 patients and fibrosis scores in 11 of 28 patients and a 2 fold reduction in the number of hepatitis C virus (HCV) specific $CD4^+$ IFNγ secreting T cells. However, there was a significant increase in HCV RNA levels which returned to baseline 6 mo after end of treatment.

A pilot open label study of rhuIL-10 in combination with glucocorticoids in 8 patients with severe AH failed to show any changes to neutrophil-derived or serum IL-8 and TNFα production[74]. No significant differences in mortality or MDF were observed in comparison to the control group. This may be explained by the fact that although in patients with severe AH IL-10 is upregulated, it is not sufficient to reduce the levels of TNFα[75]. Therefore a combination of cytokine targets to inhibit TNFα while augmenting IL-10 may be a useful approach.

IL-22, a member of the IL-10 family, shares its anti-inflammatory effects and potentiation of this molecule may be more beneficial than the use of rhuIL-10 since the IL-22 receptor is only expressed on epithelial cells such as hepatocytes. A study in a chronic ethanol-fed mouse model showed that treatment with recombinant IL-22 ameliorates liver injury and hepatic oxidative stress[76]. In a murine model of acute hepatitis IL-22 receptor is upregulated on hepatocytes and blockade of IL-22 exacerbates disease while administration of IL-22 ameliorates it[77]. Interestingly IL-22 is produced by Th17 cells, thought to be pathogenic (see below). Perhaps the strategy of blocking IL-17 in conjunction with augmenting IL-22 will have a more synergistic effect.

IL-8: Inhibition of neutrophil mediated hepatic damage may also prove to be an important therapy. Levels of *IL-8* gene expression and serum protein are elevated in patients with AH and higher levels are associated with a poorer outcome[31]. *IL-8* gene expression is also related to neutrophil hepatic infiltration as well as increased portal pressure[31]. IL-8 antagonism may reduce neutrophil recruitment into the liver without impairing the neutrophils' function in host defence and elimination of pathogens.

Hepatocyte growth factor: Hepatocyte growth factor (HGF) is thought to play an important role in the regeneration of the liver after an injury such as AH. It reduces hepatocyte apoptosis[78] as well as reducing ethanol-related oxidative damage[79]. Higher levels of HGF correlate with greater hepatocyte proliferation in AH[80] and are associated with better outcome[81]. Treatment of alcohol fed mice with recombinant HGF reduced the development of fatty liver[82]. Interestingly, HGF is produced by neutrophils and the degree of neutrophil infiltration in the liver correlates with levels of HGF[83]. Therefore a strategy of blocking neutrophil trafficking to the liver by IL-8 antagonism may also have a detrimental effect by reducing the liver's regenerative capacity. Combination of IL-8 antibodies with recombinant HGF or *HGF* gene therapy may reduce the inflammatory effects of neutrophils while maintaining the beneficial effects on hepatocyte proliferation.

T cells: T cells play a role in the recruitment of neutrophils and the perpetuation of inflammation in AH. Reduction in T cell proliferation through targeting IL-2, a T cell proliferation and survival factor, may reduce the number of pro-inflammatory cells within the inflamed liver. Inhibition of IL-2 receptor alpha (CD25) with a chimeric monoclonal antibody reverses glucocorticoid resistance *in vitro* in peripheral blood mononuclear cells from patients with AH[42]. This monoclonal antibody (basiliximab) is licensed for use in acute cellular rejection of cadaveric renal transplants. Promising results

Table 1 Summary of mechanism of action and existing evidence about potential future molecular targets for the treatment of severe alcoholic hepatitis

Treatment	Mechanism of action	Clinical evidence
rhu IL-10	Suppression of pro-inflammatory cytokines, e.g., TNFα Suppression of reactive oxygen species	Phase 2 study in severe AH with concomitant glucocorticoids showed no significant difference in mortality or levels of IL-8 and TNFα[74]
rhu IL-22	Increased levels of anti-inflammatory IL-22 Reduced oxidative stress	Reduced liver injury in ethanol-fed rat model[76] and acute hepatitis mouse model[77]. No studies in human liver disease yet reported
Anti-IL-8 antibody	Reduced neutrophil recruitment to liver	Phase 2 studies in COPD demonstrated reduced dyspnea[103]. No studies in human liver disease have yet been reported
rhu hepatocyte growth factor	Reduced hepatocyte apoptosis	HGF levels correlate with outcome in severe AH[81]. Well tolerated in a small phase 1/2 trial in fulminant hepatitis but no clear clinical benefit was seen[104]
Basiliximab (anti-CD25 antibody)	Reduced T cell proliferation and subsequent pro-inflammatory cytokine production	Reverses *in vitro* glucocorticoid resistance in patients with severe AH[42]. No clinical trials yet conducted in liver disease
Secukinumab (anti-IL-17A antibody)	Reduced pro-inflammatory IL-17A	Well tolerated in patients with rheumatoid arthritis, psoriasis or uveitis[93]. No clinical benefit in crohn's disease[94]. No clinical trial yet reported in liver disease
Anti-CXCL10 antibody	Reduced Th1 cell recruitment to liver	CXCR3 (receptor for CXCL10) is elevated in patients with chronic hepatitis C infection[95]. Phase 2 clinical trial is underway in patients with PBC

rhu: Recombinant human; AH: Alcoholic hepatitis; TNFα: Tumor necrosis factor-α; HGF: Hepatocyte growth factor; PBC: Primary biliary cirrhosis; IL: Interleukin; COPD: Chronic obstructive pulmonary disease.

from an open label study in patients with glucocorticoid resistant ulcerative colitis showed a benefit[84] but has not been borne out in a double-blind randomised controlled trial[85]. The immunogenicity of the drug together with a high achievement of clinical response and remission in the placebo arm, may have contributed to the lack of benefit over placebo in this study. However, given in a single dose (shown to be less immunogenic in renal transplant patients[86]) basiliximab may prove to be a useful adjunct to glucocorticoid therapy in patients who do not respond to this therapy.

Th17 cells: Recently, T cells producing IL-17 (known as Th17 cells) have been ascribed a central role in the pathogenesis of many inflammatory and autoimmune conditions[87] and are present in chronically inflamed tissues[88]. The generation of Th17 cells in humans requires IL-1β and IL-6 with IL-23 as a survival factor[89]. IL-17 can itself act as a neutrophil chemotaxin but can also stimulate production of other chemotaxins such as IL-8 and CXCL1[90]. To date, 6 Th17 cytokines have been described (known as IL-17A-F)[91], the most studied being IL-17A.

Serum levels of IL-17 are higher in patients with AH compared to healthy and HCV controls[92]. From the same study liver biopsy material from patients with AH showed significantly higher numbers of infiltrating IL-17$^+$ cells compared with alcohol related cirrhosis samples and the number of infiltrating cells correlated with the Maddrey Discriminant Function. The increased levels of IL-17 within the liver are likely to act on hepatic stellate cells, which when stimulated with IL-17 increase chemotaxis of neutrophils[92].

Phase 1 trials of humanised anti-IL-17A monoclonal antibody (secukinumab) have proved successful in the treatment of rheumatoid arthritis, psoriasis and uveitis[93] with phase 2 and 3 trials in rheumatoid arthritis ongoing. Disappointingly, small benefit was seen over placebo in patients with active Crohn's disease[94], which may be due to low concentration of the drug at the site of inflammation or presence of other Th17 produced cytokines such as IL-17F. To date no studies of secukinumab have been reported in patients with liver disease.

Lymphocyte trafficking to the liver

A number of chemokines and receptors have been identified as playing a role in neutrophil, macrophage or lymphocyte trafficking to the liver. Targeting these receptors or blocking their ligands could limit liver infiltration and subsequent damage leaving cells to perform other functions such as clearance of infection in the periphery. Several possible targets are appealing: CXCR3 and its ligand CXCL10 appears to be important in liver disease. CXCR3 is expressed on Th1 cells and intrahepatic CXCR3 is upregulated in patients with chronic hepatitis C infection[24,95]. Although no studies have yet been performed in AH, a monoclonal antibody to CXCL10 is currently under evaluation in patients with primary biliary cirrhosis, Crohn's disease and ulcerative colitis. However, this approach may have its limitations; a murine model of IFNγ mediated hepatitis [by Concanavalin A (ConA) challenge] demonstrated that CXCR3$^{-/-}$ mice developed a more severe hepatitis and failed to induce tolerance *via* conversion to an IL-10 secreting regulatory T cell (Treg) phenotype on re-challenge with ConA[96]. This suggests that CXCR3 is required for liver homing of lymphocytes in inflammation with subsequent development of an anti-inflammatory IL-10 secreting

Treg phenotype to limit hepatic inflammation. Therefore inhibition of the initial accumulation of T cells may lead to alteration of hepatoprotective downstream events. Combination therapy with anti-CXCL10 and rhuIL-10 or IL-22 may be an option to maintain the protective effects of IL-10 secreting Tregs.

VAP-1 is another potential target; VAP-1 is elevated in patients with inflammatory liver conditions[97] but also correlates with disease severity in AH[98]. Blockade of this molecule reduces peripheral blood and liver derived lymphocyte migration across HSECs[99].

Selective inhibition of T cell subsets, such as Th17 cells, from infiltrating the liver may reduce the most pro-inflammatory cell population from reaching the liver and causing more damage. However, the migratory fate of Th17 cells in humans is still poorly understood. Two chemokines, CCR4 and CCR6, have been identified as playing a role of Th17 migration in inflammatory disease[100,101] but these are also expressed on a variety of other T cell subsets[102]. Ongoing work is hoping to elucidate this pathway.

In conclusion, broad spectrum therapy for the treatment of severe AH has not been demonstrated to be clearly beneficial mainly due to development of infective complications. With our increasing understanding of the pathophysiology of the disease together with its immunological mechanisms, we have the opportunity to develop targeted molecular approaches (Table 1). However, work on AH remains challenging in the absence of an appropriate animal model. Many of the pre-clinical studies use chronic ethanol feeding murine models or we must infer results from non-alcoholic models of acute liver injury such as ischaemic or carbon tetrachloride induced hepatitis. This deficit must be addressed so we can further our understanding of the pathogenesis of this disease. Furthermore, clinical studies in AH lag far behind other inflammatory and autoimmune conditions such as rheumatoid arthritis and Crohn's disease. Learning from these studies we have seen that selected cytokine inhibition has rarely been successful (with TNFα being a notable exception). We therefore would strongly endorse future assessment of combination therapy such as recombinant IL-10 or IL-22 with anti-IL-17, HGF with anti-IL-8, glucocorticoids with IL-10, IL-22 or anti-CD25 or selective inhibition of chemokines and cytokines within the liver.

REFERENCES

1 **World Health Organization**. Global status report on alcohol and health. Geneva: World Helath Organization Press, 2011
2 **Rehm J**, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009; **373**: 2223-2233
3 **The Health and Social Care Information Centre**. Statistics on alcohol, England: 2010. London: The Health and Social Care *Information Centre*, 2010
4 **Maddrey WC**, Boitnott JK, Bedine MS, Weber FL, Mezey E, White RI. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978; **75**: 193-199
5 **Mathurin P**, O'Grady J, Carithers RL, Phillips M, Louvet A, Mendenhall CL, Ramond MJ, Naveau S, Maddrey WC, Morgan TR. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. *Gut* 2011; **60**: 255-260
6 **Lieber CS**, DeCarli LM, Sorrell MF. Experimental methods of ethanol administration. *Hepatology* 1989; **10**: 501-510
7 **Reep GL**, Soloway RD. Recent and currently emerging medical treatment options for the treatment of alcoholic hepatitis. *World J Hepatol* 2011; **3**: 211-214
8 **Rongey C**, Kaplowitz N. Current concepts and controversies in the treatment of alcoholic hepatitis. *World J Gastroenterol* 2006; **12**: 6909-6921
9 **Singal AK**, Walia I, Singal A, Soloway RD. Corticosteroids and pentoxifylline for the treatment of alcoholic hepatitis: Current status. *World J Hepatol* 2011; **3**: 205-210
10 **Setshedi M**, Wands JR, Monte SM. Acetaldehyde adducts in alcoholic liver disease. *Oxid Med Cell Longev* 2010; **3**: 178-185
11 **Yan AW**, Fouts DE, Brandl J, Stärkel P, Torralba M, Schott E, Tsukamoto H, Nelson KE, Brenner DA, Schnabl B. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology* 2011; **53**: 96-105
12 **Bode C**, Bode JC. Effect of alcohol consumption on the gut. *Best Pract Res Clin Gastroenterol* 2003; **17**: 575-592
13 **Ma TY**, Nguyen D, Bui V, Nguyen H, Hoa N. Ethanol modulation of intestinal epithelial tight junction barrier. *Am J Physiol* 1999; **276**: G965-G974
14 **Rao R**. Endotoxemia and gut barrier dysfunction in alcoholic liver disease. *Hepatology* 2009; **50**: 638-644
15 **Fukui H**, Brauner B, Bode JC, Bode C. Plasma endotoxin concentrations in patients with alcoholic and non-alcoholic liver disease: reevaluation with an improved chromogenic assay. *J Hepatol* 1991; **12**: 162-169
16 **Uesugi T**, Froh M, Arteel GE, Bradford BU, Thurman RG. Toll-like receptor 4 is involved in the mechanism of early alcohol-induced liver injury in mice. *Hepatology* 2001; **34**: 101-108
17 **Adachi Y**, Moore LE, Bradford BU, Gao W, Thurman RG. Antibiotics prevent liver injury in rats following long-term exposure to ethanol. *Gastroenterology* 1995; **108**: 218-224
18 **Nanji AA**, Khettry U, Sadrzadeh SM. Lactobacillus feeding reduces endotoxemia and severity of experimental alcoholic liver (disease). *Proc Soc Exp Biol Med* 1994; **205**: 243-247
19 **Chedid A**, Mendenhall CL, Moritz TE, French SW, Chen TS, Morgan TR, Roselle GA, Nemchausky BA, Tamburro CH, Schiff ER. Cell-mediated hepatic injury in alcoholic liver disease. Veterans Affairs Cooperative Study Group 275. *Gastroenterology* 1993; **105**: 254-266
20 **Adams DH**, Hubscher SG, Fisher NC, Williams A, Robinson M. Expression of E-selectin and E-selectin ligands in human liver inflammation. *Hepatology* 1996; **24**: 533-538
21 **Lalor PF**, Edwards S, McNab G, Salmi M, Jalkanen S, Adams DH. Vascular adhesion protein-1 mediates adhesion and transmigration of lymphocytes on human hepatic endothelial cells. *J Immunol* 2002; **169**: 983-992
22 **Curbishley SM**, Eksteen B, Gladue RP, Lalor P, Adams DH. CXCR 3 activation promotes lymphocyte transendothelial migration across human hepatic endothelium under fluid flow. *Am J Pathol* 2005; **167**: 887-899
23 **Holt AP**, Haughton EL, Lalor PF, Filer A, Buckley CD, Adams DH. Liver myofibroblasts regulate infiltration and positioning of lymphocytes in human liver. *Gastroenterology* 2009; **136**: 705-714
24 **Shields PL**, Morland CM, Salmon M, Qin S, Hubscher SG, Adams DH. Chemokine and chemokine receptor interactions provide a mechanism for selective T cell recruitment to specific liver compartments within hepatitis C-infected liver. *J Immunol* 1999; **163**: 6236-6243
25 **Kim CH**, Rott L, Kunkel EJ, Genovese MC, Andrew DP, Wu

L, Butcher EC. Rules of chemokine receptor association with T cell polarization in vivo. *J Clin Invest* 2001; **108**: 1331-1339
26 **Cao Q**, Batey R, Pang G, Clancy R. Ethanol-altered liver-associated T cells mediate liver injury in rats administered Concanavalin A (Con A) or lipopolysaccharide (LPS). *Alcohol Clin Exp Res* 1999; **23**: 1660-1667
27 **Natori S**, Rust C, Stadheim LM, Srinivasan A, Burgart LJ, Gores GJ. Hepatocyte apoptosis is a pathologic feature of human alcoholic hepatitis. *J Hepatol* 2001; **34**: 248-253
28 **Ziol M**, Tepper M, Lohez M, Arcangeli G, Ganne N, Christidis C, Trinchet JC, Beaugrand M, Guillet JG, Guettier C. Clinical and biological relevance of hepatocyte apoptosis in alcoholic hepatitis. *J Hepatol* 2001; **34**: 254-260
29 **Maltby J**, Wright S, Bird G, Sheron N. Chemokine levels in human liver homogenates: associations between GRO alpha and histopathological evidence of alcoholic hepatitis. *Hepatology* 1996; **24**: 1156-1160
30 **Bajt ML**, Farhood A, Jaeschke H. Effects of CXC chemokines on neutrophil activation and sequestration in hepatic vasculature. *Am J Physiol Gastrointest Liver Physiol* 2001; **281**: G1188-G1195
31 **Dominguez M**, Miquel R, Colmenero J, Moreno M, García-Pagán JC, Bosch J, Arroyo V, Ginès P, Caballería J, Bataller R. Hepatic expression of CXC chemokines predicts portal hypertension and survival in patients with alcoholic hepatitis. *Gastroenterology* 2009; **136**: 1639-1650
32 **Jaeschke H**. Kupffer cell-induced oxidant stress during hepatic ischemia-reperfusion: does the controversy continue? *Hepatology* 1999; **30**: 1527-1528
33 **Barnes PJ**, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med* 1997; **336**: 1066-1071
34 **Taïeb J**, Mathurin P, Elbim C, Cluzel P, Arce-Vicioso M, Bernard B, Opolon P, Gougerot-Pocidalo MA, Poynard T, Chollet-Martin S. Blood neutrophil functions and cytokine release in severe alcoholic hepatitis: effect of corticosteroids. *J Hepatol* 2000; **32**: 579-586
35 **Christensen E**, Gluud C. Glucocorticoids are ineffective in alcoholic hepatitis: a meta-analysis adjusting for confounding variables. *Gut* 1995; **37**: 113-118
36 **Imperiale TF**, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. *Ann Intern Med* 1990; **113**: 299-307
37 **National Institute for Health and Clinical Excellence**. Alcohol use disorders: diagnosis and clinical management of alcohol-related physical complications. CG100. London: National Institute for Health and Clinical Excellence, 2010
38 **Mendenhall CL**, Anderson S, Garcia-Pont P, Goldberg S, Kiernan T, Seeff LB, Sorrell M, Tamburro C, Weesner R, Zetterman R. Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. *N Engl J Med* 1984; **311**: 1464-1470
39 **Ramond MJ**, Poynard T, Rueff B, Mathurin P, Théodore C, Chaput JC, Benhamou JP. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *N Engl J Med* 1992; **326**: 507-512
40 **Mathurin P**, Duchatelle V, Ramond MJ, Degott C, Bedossa P, Erlinger S, Benhamou JP, Chaput JC, Rueff B, Poynard T. Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. *Gastroenterology* 1996; **110**: 1847-1853
41 **Louvet A**, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, Dharancy S, Texier F, Hollebecque A, Serfaty L, Boleslawski E, Deltenre P, Canva V, Pruvot FR, Mathurin P. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology* 2007; **45**: 1348-1354
42 **di Mambro AJ**, Parker R, McCune A, Gordon F, Dayan CM, Collins P. In vitro steroid resistance correlates with outcome in severe alcoholic hepatitis. *Hepatology* 2011; **53**: 1316-1322
43 **Doherty GM**, Jensen JC, Alexander HR, Buresh CM, Norton JA. Pentoxifylline suppression of tumor necrosis factor gene transcription. *Surgery* 1991; **110**: 192-198
44 **Han J**, Thompson P, Beutler B. Dexamethasone and pentoxifylline inhibit endotoxin-induced cachectin/tumor necrosis factor synthesis at separate points in the signaling pathway. *J Exp Med* 1990; **172**: 391-394
45 **Zabel P**, Schönharting MM, Schade UF, Schlaak M. Effects of pentoxifylline in endotoxinemia in human volunteers. *Prog Clin Biol Res* 1991; **367**: 207-213
46 **Akriviadis E**, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119**: 1637-1648
47 **Raetsch C**, Jia JD, Boigk G, Bauer M, Hahn EG, Riecken EO, Schuppan D. Pentoxifylline downregulates profibrogenic cytokines and procollagen I expression in rat secondary biliary fibrosis. *Gut* 2002; **50**: 241-247
48 **De BK**, Gangopadhyay S, Dutta D, Baksi SD, Pani A, Ghosh P. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. *World J Gastroenterol* 2009; **15**: 1613-1619
49 **Whitfield K**, Rambaldi A, Wetterslev J, Gluud C. Pentoxifylline for alcoholic hepatitis. *Cochrane Database Syst Rev* 2009; (4): CD007339
50 **Dey A**, Cederbaum AI. Alcohol and oxidative liver injury. *Hepatology* 2006; **43**: S63-S74
51 **Nguyen-Khac E**, Thevenot T, Piquet MA, Benferhat S, Goria O, Chatelain D, Tramier B, Dewaele F, Ghrib S, Rudler M, Carbonell N, Tossou H, Bental A, Bernard-Chabert B, Dupas JL. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. *N Engl J Med* 2011; **365**: 1781-1789
52 **Stewart S**, Prince M, Bassendine M, Hudson M, James O, Jones D, Record C, Day CP. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. *J Hepatol* 2007; **47**: 277-283
53 **Phillips M**, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis--a randomised clinical trial. *J Hepatol* 2006; **44**: 784-790
54 **Mezey E**, Potter JJ, Rennie-Tankersley L, Caballeria J, Pares A. A randomized placebo controlled trial of vitamin E for alcoholic hepatitis. *J Hepatol* 2004; **40**: 40-46
55 **Maini R**, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999; **354**: 1932-1939
56 **Targan SR**, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337**: 1029-1035
57 **Bird GL**, Sheron N, Goka AK, Alexander GJ, Williams RS. Increased plasma tumor necrosis factor in severe alcoholic hepatitis. *Ann Intern Med* 1990; **112**: 917-920
58 **Rodríguez-Rodríguez E**, González-Reimers E, Santolaria-Fernández F, Milena-Abril A, Rodríguez-Moreno F, Oramas-Rodríguez J, Martínez-Riera A. Cytokine levels in acute alcoholic hepatitis: a sequential study. *Drug Alcohol Depend* 1995; **39**: 23-27
59 **Felver ME**, Mezey E, McGuire M, Mitchell MC, Herlong HF, Veech GA, Veech RL. Plasma tumor necrosis factor alpha predicts decreased long-term survival in severe alcoholic hepatitis. *Alcohol Clin Exp Res* 1990; **14**: 255-259
60 **Iimuro Y**, Gallucci RM, Luster MI, Kono H, Thurman RG. Antibodies to tumor necrosis factor alfa attenuate hepatic necrosis and inflammation caused by chronic exposure to

ethanol in the rat. *Hepatology* 1997; **26**: 1530-1537
61 **Spahr L**, Rubbia-Brandt L, Frossard JL, Giostra E, Rougemont AL, Pugin J, Fischer M, Egger H, Hadengue A. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. *J Hepatol* 2002; **37**: 448-455
62 **Naveau S**, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, Davion T, Oberti F, Broët P, Emilie D. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. *Hepatology* 2004; **39**: 1390-1397
63 **Boetticher NC**, Peine CJ, Kwo P, Abrams GA, Patel T, Aqel B, Boardman L, Gores GJ, Harmsen WS, McClain CJ, Kamath PS, Shah VH. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. *Gastroenterology* 2008; **135**: 1953-1960
64 **Loguercio C**, Federico A, Tuccillo C, Terracciano F, D'Auria MV, De Simone C, Del Vecchio Blanco C. Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases. *J Clin Gastroenterol* 2005; **39**: 540-543
65 **Kirpich IA**, Solovieva NV, Leikhter SN, Shidakova NA, Lebedeva OV, Sidorov PI, Bazhukova TA, Soloviev AG, Barve SS, McClain CJ, Cave M. Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: a pilot study. *Alcohol* 2008; **42**: 675-682
66 **Sanyal A**, Younossi ZM, Bass NM, Mullen KD, Poordad F, Brown RS, Vemuru RP, Mazen Jamal M, Huang S, Merchant K, Bortey E, Forbes WP. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2011; **34**: 853-861
67 **Fuchs AC**, Granowitz EV, Shapiro L, Vannier E, Lonnemann G, Angel JB, Kennedy JS, Rabson AR, Radwanski E, Affrime MB, Cutler DL, Grint PC, Dinarello CA. Clinical, hematologic, and immunologic effects of interleukin-10 in humans. *J Clin Immunol* 1996; **16**: 291-303
68 **Xystrakis E**, Kusumakar S, Boswell S, Peek E, Urry Z, Richards DF, Adikibi T, Pridgeon C, Dallman M, Loke TK, Robinson DS, Barrat FJ, O'Garra A, Lavender P, Lee TH, Corrigan C, Hawrylowicz CM. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. *J Clin Invest* 2006; **116**: 146-155
69 **Fedorak RN**, Gangl A, Elson CO, Rutgeerts P, Schreiber S, Wild G, Hanauer SB, Kilian A, Cohard M, LeBeaut A, Feagan B. Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group. *Gastroenterology* 2000; **119**: 1473-1482
70 **Schreiber S**, Fedorak RN, Nielsen OH, Wild G, Williams CN, Nikolaus S, Jacyna M, Lashner BA, Gangl A, Rutgeerts P, Isaacs K, van Deventer SJ, Koningsberger JC, Cohard M, LeBeaut A, Hanauer SB. Safety and efficacy of recombinant human interleukin 10 in chronic active Crohn's disease. Crohn's Disease IL-10 Cooperative Study Group. *Gastroenterology* 2000; **119**: 1461-1472
71 **Buruiana FE**, Solà I, Alonso-Coello P. Recombinant human interleukin 10 for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2010; (11): CD005109
72 **Tilg H**, van Montfrans C, van den Ende A, Kaser A, van Deventer SJ, Schreiber S, Gregor M, Ludwiczek O, Rutgeerts P, Gasche C, Koningsberger JC, Abreu L, Kuhn I, Cohard M, LeBeaut A, Grint P, Weiss G. Treatment of Crohn's disease with recombinant human interleukin 10 induces the proinflammatory cytokine interferon gamma. *Gut* 2002; **50**: 191-195
73 **Nelson DR**, Tu Z, Soldevila-Pico C, Abdelmalek M, Zhu H, Xu YL, Cabrera R, Liu C, Davis GL. Long-term interleukin 10 therapy in chronic hepatitis C patients has a proviral and anti-inflammatory effect. *Hepatology* 2003; **38**: 859-868
74 **Taieb J**, Chollet-Martin S, Delarche C, Cohard M, LeBeaut A, Cluzel P, Bernard B, Gougerot-Pocidalo MA, Poynard T. Subcutaneous interleukin-10 plus corticosteroids in the treatment of severe alcoholic hepatitis. Results of a pilot study. *Hepatology* 2003; **38** (Suppl 2): 202
75 **Naveau S**, Balian A, Capron F, Raynard B, Fallik D, Agostini H, Grangeot-Keros L, Portier A, Galanaud P, Chaput JC, Emilie D. Balance between pro and anti-inflammatory cytokines in patients with acute alcoholic hepatitis. *Gastroenterol Clin Biol* 2005; **29**: 269-274
76 **Ki SH**, Park O, Zheng M, Morales-Ibanez O, Kolls JK, Bataller R, Gao B. Interleukin-22 treatment ameliorates alcoholic liver injury in a murine model of chronic-binge ethanol feeding: role of signal transducer and activator of transcription 3. *Hepatology* 2010; **52**: 1291-1300
77 **Radaeva S**, Sun R, Pan HN, Hong F, Gao B. Interleukin 22 (IL-22) plays a protective role in T cell-mediated murine hepatitis: IL-22 is a survival factor for hepatocytes via STAT3 activation. *Hepatology* 2004; **39**: 1332-1342
78 **Huh CG**, Factor VM, Sánchez A, Uchida K, Conner EA, Thorgeirsson SS. Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. *Proc Natl Acad Sci USA* 2004; **101**: 4477-4482
79 **Valdés-Arzate A**, Luna A, Bucio L, Licona C, Clemens DL, Souza V, Hernandez E, Kershenobich D, Gutiérrez-Ruiz MC, Gómez-Quiroz LE. Hepatocyte growth factor protects hepatocytes against oxidative injury induced by ethanol metabolism. *Free Radic Biol Med* 2009; **47**: 424-430
80 **Hillan KJ**, Logan MC, Ferrier RK, Bird GL, Bennett GL, McKay IC, MacSween RN. Hepatocyte proliferation and serum hepatocyte growth factor levels in patients with alcoholic hepatitis. *J Hepatol* 1996; **24**: 385-390
81 **Fang JW**, Bird GL, Nakamura T, Davis GL, Lau JY. Hepatocyte proliferation as an indicator of outcome in acute alcoholic hepatitis. *Lancet* 1994; **343**: 820-823
82 **Tahara M**, Matsumoto K, Nukiwa T, Nakamura T. Hepatocyte growth factor leads to recovery from alcohol-induced fatty liver in rats. *J Clin Invest* 1999; **103**: 313-320
83 **Taïeb J**, Delarche C, Paradis V, Mathurin P, Grenier A, Crestani B, Dehoux M, Thabut D, Gougerot-Pocidalo MA, Poynard T, Chollet-Martin S. Polymorphonuclear neutrophils are a source of hepatocyte growth factor in patients with severe alcoholic hepatitis. *J Hepatol* 2002; **36**: 342-348
84 **Creed TJ**, Norman MR, Probert CS, Harvey RF, Shaw IS, Smithson J, Anderson J, Moorghen M, Gupta J, Shepherd NA, Dayan CM, Hearing SD. Basiliximab (anti-CD25) in combination with steroids may be an effective new treatment for steroid-resistant ulcerative colitis. *Aliment Pharmacol Ther* 2003; **18**: 65-75
85 **Sands BE**, Sandborn WJ, Creed T, Dayan CM, Dhanda AD, Van Assche GA, Gregus M, Sood A, Choudhuri G, Stempien MJ, Levitt D, Probert C. Basiliximab Does Not Increase Efficacy of Corticosteroids in Patients with Steroid-Refractory Ulcerative Colitis. *Gastroenterology* 2012; **143**: 356-364.e1
86 **Kovarik J**, Wolf P, Cisterne JM, Mourad G, Lebranchu Y, Lang P, Bourbigot B, Cantarovich D, Girault D, Gerbeau C, Schmidt AG, Soulillou JP. Disposition of basiliximab, an interleukin-2 receptor monoclonal antibody, in recipients of mismatched cadaver renal allografts. *Transplantation* 1997; **64**: 1701-1705
87 **Korn T**, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. *Annu Rev Immunol* 2009; **27**: 485-517
88 **Pène J**, Chevalier S, Preisser L, Vénéreau E, Guilleux MH, Ghannam S, Molès JP, Danger Y, Ravon E, Lesaux S, Yssel H, Gascan H. Chronically inflamed human tissues are infiltrated by highly differentiated Th17 lymphocytes. *J Immunol* 2008; **180**: 7423-7430
89 **Wilson NJ**, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, Basham B, Smith K, Chen T, Morel F, Lecron JC, Kastelein RA, Cua DJ, McClanahan TK, Bowman EP, de Waal Malefyt R. Development, cytokine profile and

function of human interleukin 17-producing helper T cells. *Nat Immunol* 2007; **8**: 950-957
90 **Jones CE**, Chan K. Interleukin-17 stimulates the expression of interleukin-8, growth-related oncogene-alpha, and granulocyte-colony-stimulating factor by human airway epithelial cells. *Am J Respir Cell Mol Biol* 2002; **26**: 748-753
91 **Gaffen SL**. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol* 2009; **9**: 556-567
92 **Lemmers A**, Moreno C, Gustot T, Maréchal R, Degré D, Demetter P, de Nadai P, Geerts A, Quertinmont E, Vercruysse V, Le Moine O, Devière J. The interleukin-17 pathway is involved in human alcoholic liver disease. *Hepatology* 2009; **49**: 646-657
93 **Hueber W**, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G, Antoni C, Draelos Z, Gold MH, Durez P, Tak PP, Gomez-Reino JJ, Foster CS, Kim RY, Samson CM, Falk NS, Chu DS, Callanan D, Nguyen QD, Rose K, Haider A, Di Padova F. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci Transl Med* 2010; **2**: 52ra72
94 **Hueber W**, Sands BE, Vandemeulebroecke M, Reinisch W, Higgins PDR, Wehkamp J, Feagan B, Yao M, Bertolino AP, Travis S. Inhibition of IL-17A by secukinumab is ineffective for Crohn's disease. *J Crohns Colitis* 2011; **5**: S7
95 **Zeremski M**, Petrovic LM, Chiriboga L, Brown QB, Yee HT, Kinkhabwala M, Jacobson IM, Dimova R, Markatou M, Talal AH. Intrahepatic levels of CXCR3-associated chemokines correlate with liver inflammation and fibrosis in chronic hepatitis C. *Hepatology* 2008; **48**: 1440-1450
96 **Erhardt A**, Wegscheid C, Claass B, Carambia A, Herkel J, Mittrücker HW, Panzer U, Tiegs G. CXCR3 deficiency exacerbates liver disease and abrogates tolerance in a mouse model of immune-mediated hepatitis. *J Immunol* 2011; **186**: 5284-5293
97 **Kurkijärvi R**, Yegutkin GG, Gunson BK, Jalkanen S, Salmi M, Adams DH. Circulating soluble vascular adhesion protein 1 accounts for the increased serum monoamine oxidase activity in chronic liver disease. *Gastroenterology* 2000; **119**: 1096-1103
98 **Lalor PF**, Tuncer C, Weston C, Martin-Santos A, Smith DJ, Adams DH. Vascular adhesion protein-1 as a potential therapeutic target in liver disease. *Ann N Y Acad Sci* 2007; **1110**: 485-496
99 **Martelius T**, Salaspuro V, Salmi M, Krogerus L, Höckerstedt K, Jalkanen S, Lautenschlager I. Blockade of vascular adhesion protein-1 inhibits lymphocyte infiltration in rat liver allograft rejection. *Am J Pathol* 2004; **165**: 1993-2001
100 **Hirota K**, Yoshitomi H, Hashimoto M, Maeda S, Teradaira S, Sugimoto N, Yamaguchi T, Nomura T, Ito H, Nakamura T, Sakaguchi N, Sakaguchi S. Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model. *J Exp Med* 2007; **204**: 2803-2812
101 **Kim CH**. Migration and function of Th17 cells. *Inflamm Allergy Drug Targets* 2009; **8**: 221-228
102 **Lim HW**, Lee J, Hillsamer P, Kim CH. Human Th17 cells share major trafficking receptors with both polarized effector T cells and FOXP3+ regulatory T cells. *J Immunol* 2008; **180**: 122-129
103 **Mahler DA**, Huang S, Tabrizi M, Bell GM. Efficacy and safety of a monoclonal antibody recognizing interleukin-8 in COPD: a pilot study. *Chest* 2004; **126**: 926-934
104 **Ido A**, Moriuchi A, Numata M, Murayama T, Teramukai S, Marusawa H, Yamaji N, Setoyama H, Kim ID, Chiba T, Higuchi S, Yokode M, Fukushima M, Shimizu A, Tsubouchi H. Safety and pharmacokinetics of recombinant human hepatocyte growth factor (rh-HGF) in patients with fulminant hepatitis: a phase I/II clinical trial, following preclinical studies to ensure safety. *J Transl Med* 2011; **9**: 55

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