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.

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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 2006[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
Alcohol is known to change the gut microbiota, leading to a direct toxic effect of alcohol on the liver that causes DNA damage (see Setshedi et al[10]). However, it is not only the direct toxic effect of alcohol on the liver that causes DNA damage (see Setshedi et al[10]). 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[17,18]. 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 innate 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 veins 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[19]. 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 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[18]. Therefore, at present we must interpret results from these studies with caution and focus attention on studies on human tissue.

It is clear that alcohol acts both directly on the liver, causing cell death by toxic mediators, and via activation of the innate 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[18]. 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[17,18]. We have emphasised the molecules that we believe have the greatest future therapeutic potential.

**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[20,21] 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 reduces 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
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 [30], IL-8 and monocyte chemoattractant protein 2 [31]. CXC chemokines are particularly important for neutrophil infiltration in AH [32]. 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[36].

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[39]. Another trial recruiting only patients with histologically proven AH showed a survival benefit with glucocorticoid treatment at 2 mo but no difference at long term follow-up at 2 years[40,41]. More recent meta-analysis of individual patient data demonstrated a survival benefit with glucocorticoid treatment in patients with severe AH[42]. However, they identify a proportion of glucocorticoid non-responders, with a significantly worse outcome, by applying the Lille model[40] 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- and long-term survival[58], 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[59] 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[59]. 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[59]. An RCT of etanercept also found that there was a significantly poorer outcome for patients on active treatment due to infection[60]. 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

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such as rifaximin may also be beneficial and has recently been proven effective for the prevention of hepatic encephalopathy in patients with cirrhosis\(^{[50]}\).

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 kuppfer cells. IL-10 can also inhibit production of reactive oxygen species by neutrophils\(^{[69]}\). 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\(^{[90]}\). 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\(^{[31]}\) 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\(^{[74]}\). 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\(^{[58]}\). 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\(^{[74]}\). 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\(^{[80]}\). IL-8 gene expression is also related to neutrophil hepatic infiltration as well as increased portal pressure\(^{[80]}\). 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\(^{[81]}\) as well as reducing ethanol-related oxidative damage\(^{[79]}\). Higher levels of HGF correlate with greater hepatocyte proliferation in AH\(^{[81]}\) and are associated with better outcome\(^{[83]}\). Treatment of alcohol fed mice with recombinant HGF reduced the development of fatty liver\(^ { [84] }\). 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\(^{[85]}\). 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                                | Phase 2 study in severe AH with concomitant glucocorticoids showed no significant difference in mortality or levels of IL-8 and TNFα[80]          |
| rhu IL-22                        | Increased levels of anti-inflammatory IL-22                                          | Reduced liver injury in ethanol-fed rat model[89] and acute hepatitis mouse model[89]. 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[88]. 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[83]. Well tolerated in a small phase 1/2 trial in fulminant hepatitis but no clear clinical benefit was seen[83] |
| Basiliximab (anti-CD25 antibody) | Reduced T cell proliferation and subsequent pro-inflammatory cytokine production    | Reverses in vitro glucocorticoid resistance in patients with severe AHP[82]. 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[84]. No clinical benefit in Crohn’s disease[84]. 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[96]. 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[88]. 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[88]) 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[92] 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[93]. IL-17 can itself act as a neutrophil chemotaxin but can also stimulate production of other chemotaxins such as IL-8 and CXCL1[94]. To date, 6 Th17 cytokines have been described (known as IL-17A-F)[94], the most studied being IL-17A.

Serum levels of IL-17 are higher in patients with AH compared to healthy and HCV controls[89]. 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[81].

Phase 1 trials of humanised anti-IL-17A monoclonal antibody (secukinumab) have proved successful in the treatment of rheumatoid arthritis, psoriasis and uveitis 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[95,96]. 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 re-challenge with ConA[97]. This suggests that CXCR3 is required for liver homing of lymphocytes in inflammation with subsequent development of an anti-inflammatory IL-10 secreting mechanism.
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 theprotective effects of IL-10 secreting Tregs.

VAP-1 is another potential target; VAP-1 is elevated in patients with inflammatory liver conditions[7] but also correlates with disease severity in AH[8]. Blockade of this molecule reduces peripheral blood and liver derived lymphocyte migration across HSECs[9].

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[10,11], but these are also expressed on a variety of other T cell subsets[12]. 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 TNF 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.

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