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Inhibition of TNFa in Patients with Concomitant HCV Infection; Molecular Insights and Safety

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Abstract

Chronic viral infections, such as chronic hepatitis C, are major causes of disease worldwide. They represent model systems for the study both of sophisticated ways to elute host defense mechanisms, and of mechanisms to sustain inflammation, potentially leading to autoimmune manifestations as a side effect. Cytokines are central inducers and regulators of both immune-mediated virus clearance and of immunopathology. This review describes the potential implications of TNFa in the development and clinical progression of chronic hepatitis C infection. The frequency of chronic hepatitis C, its usually indolent course, and the current application of these biological agents for the management of continuously expanding therapeutic indices, renders the study of the molecular effects and safety of TNFa antagonists in chronic HCV carriers of particular clinical significance.

Hepatitis C Infection; Epidemiology and Clinical Course of the Disease

Hepatitis C represents the main cause of chronic liver disease; the estimated global prevalence is about 2.2%, affecting more than 150-170 million people worldwide. Chronic hepatitis C infection is directly associated with cirrhosis and the post-cirrhotic development of hepatocellular carcinoma [1].

HCV-infected patients serve as the reservoir for transmission to others. Transmission rates are reported to be much higher in IDU and hospital-based populations than among the general population, with the highest rates of new infections appearing within the first years of injecting [2].

Both geographical and temporal differences exist in the pattern of HCV infection. The highest prevalence rate has been recorded in Northern Africa (>2.9%; Egypt) and the lowest in the United Kingdom and Scandinavia (0.01%-0.1%). Moreover, endemic strains, characterized by their viral genotype, have persisted in specific areas for long periods. In the developed countries, the highest prevalence rates have been recorded among the age groups of 20-49 years, while in the developing countries the prevalence rate seems to increase steadily with age, consistent with the age-dependent risk factors for transmission in the corresponding countries [3].

Despite the large numbers of HCV patients affected worldwide, the lack of general symptomatology, especially in the initial phases, and the indolent course of the disease, render it difficult to map the clinical course of the infection. Acute hepatitis C is rare. More than 80% of the affected individuals develop chronic infection; 10% to 20% develop spontaneous clearance with natural immunity [4,5]. Viral clearance typically presents within the first 6 months of infection. Some patients show a relapsing course of the infection during the same period, followed by persistence. This may be due to superinfection or infection with multiple strains [6]. Among several factors assessed for disease progression and development of cirrhosis, age (but not age at infection), alcohol consumption and persistent elevation of ALT were found to be important for prediction of occurrence of cirrhosis [7-9].

The Role of Innate and Adaptive Immunity in HCV Infection

HCV infection is defined as the detection of specific antibodies in the serum, with or without detectable HCV-specific RNA, and is associated with ongoing or resolved infection respectively. Seroconversion in the absence of detectable HCV RNA is usually an incidental finding, indicating that resolution of HCV infection occurs in the majority of cases without treatment, through innate and/or adaptive immune responses [10].

The most important anti-viral defense mechanism in the viral clearing process is the production of type I Interferons (IFNs) and the subsequent induction of IFN-stimulated genes and cellular interactions. The pivotal role of T cell response is indicated by the detection of HCV specific $CD4^+$ and $CD8^+$ responses even in the absence of detectable seroconversion, suggesting that the T cell mediated response may occasionally suffice for efficient HCV infection resolution [11]. Moreover, viral clearance has been reported in agammaglobulinaemic patients [12].

The role of T lymphocytes in the clearing process of the virus is further supported by HLA association with outcome—eg HLA B27, HLA B57, HLA A3 and HLA DR11 [13].

Antigen presenting cells such as monocytes and dendritic cells also recognize viral antigens, resulting in activation and production of defensins and pentraxins, and of pro-inflammatory cytokines, such as IL-6, TNF-a, IL-1a and IL-1b. These cytokines in turn themselves induce production of acute phase proteins in hepatocytes such as complement components, pentraxins, and defensins, which contribute to clearance of viruses and infected cells [14].

Despite the leading role of innate immunity, adaptive immunity is also considered to contribute significantly to spontaneous clearance. Mean time to seroconversion is usually about 6 weeks after the onset of

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viraemia. The antibody response is generally of low titer, and primarily restricted to the IgG1 subclass [15].

Autoimmune Manifestations of Chronic HCV Infection

Hepatitis C virus is not only hepatotropic, but also lymphotropic. Chronic hepatitis C virus infection has been associated with a variety of lymphoproliferative disorders, ranging from cryoglobulinemia, to monoclonal gammopathies and the development of B-cell lymphomas [16]. As a consequence, patients with chronic hepatitis C virus infection very often develop extrahepatic (autoimmune) manifestations (>70% of HCV patients) [17,18].

Several serological immunologic abnormalities have frequently been observed in these patients, including cryoglobulins, the presence of rheumatoid factor, antinuclear antibodies (ANA) with speckled immunofluorescence pattern, anti-smooth muscle antibodies (ASMA), low thyroxine levels, and more rarely, positivity for anti-neutrophil cytoplamic (ANCA) antibodies. However, autoantibodies in chronic hepatitis C virus infection are usually detected in low titers and are rarely accompanied by analogous clinical syndromes, eg ANCA vasculitis.

Extrahepatic autoimmune diseases associated with hepatitis C virus infection include cryoglobulinemia, autoimmune thyroiditis, Sjogren's syndrome, lichen planus, Crest syndrome (~1% of HCV patients are positive for anti-centromere antibodies ACA, a proportion of which may develop Crest syndrome), and autoimmune cytopenia. Manifestations not always connected to a full blown syndrome include pruritus, sicca syndrome, myalgias, paresthesias, arthralgias, and, less frequently, psoriasis and Raynaud's phenomenon.

The range of extrahepatic manifestations in HCV infection validates HCV as a systemic disease. Geographic, environmental and genetic factors together with disease activity appear to contribute to the development of these manifestations. Recently, a predilection for the development of autoimmune manifestations, such as mixed cryoglobulinemia, and response to treatment, was suggested among genetically predisposed patients (carriers of FcγR and BAFF promoter polymorphisms) [19].

Under circumstances, etiologic treatment used to eradicate the virus may itself evoke specific extrahepatic manifestations, eg interferon.

Inflammation in Chronic Hepatitis C; Friend or Foe?

The fact that the majority of the infected patients develop a chronic infection clearly indicates that HCV has evolved sophisticated escape strategies to evade both the innate and the adaptive immune system. Thus, chronic hepatitis C is characterized by perturbations in the number, subset composition and/or functionality of natural killer cells, natural killer T cells, dendritic cells, macrophages and T cells; progression to chronic hepatitis C is associated with weak and narrow T cell responses to the virus [20,21]. The balance between HCV-induced immune evasion and the antiviral immune response results in histologically verified chronic inflammation in the liver, and consequent immune-mediated liver injury, as well as chronic inflammation in extrahepatic sites [22].

Constitutive chemokine production is a key mechanism for the perpetuation of inflammation [23]. Augmented constitutive release of chemokines triggered by persistent viral replication results in recruitment of virus-specific and non-specific inflammatory cells to the liver, and subsequent chronic liver injury without, however, efficient clearance of the virus. In support of the direct link of cytokine expression with the degree of inflammation, certain polymorphisms of cytokine-related genes were found to be directly related to the level of inflammation, as defined by alanine transaminase (ALT) levels and subsequent progression of liver fibrosis [24].

In a recent study including Chinese patients or healthy controls respectively, serum levels of several cytokines were measured and related to spontaneous clearance of HCV virus or to the development of chronic infection respectively. IFN-γ and IL-6 were significantly lower in chronic infection, along with continuing viral replication and disease progression, while levels of TNF-α, IL-2, IL-10 and IL-4 were not found to differ significantly in patients with chronic hepatitis C (CHC), when compared with individuals with spontaneously resolved infection [25]. In the same study, serum levels of IL-33 were correlated with the concentrations of ALT and aspartate transaminase (AST) in chonic hepatitis C patients, and were found to be significantly higher than those detected in resolved infection and healthy controls; levels decreased after treatment with interferon for 12 weeks. Finally, elevated levels of TNFa were reported in chronic hepatitis patients with extrahepatic manifestations, and correlated with progression to liver fibrosis [26,27]. Despite its association with increased levels of inflammation in CHC, in the case of TNFa, polymorphisms were not found in meta analyses to be related to susceptibility to the virus, viral clearance or progression to chronicity [28]. Other studies indicated a positive association of specific TNFa gene promoter polymorphisms with response to treatment and viral clearance [29]; hence more clinical evidence is needed to draw firm conclusions.

The Role of TNFa in Chronic Hepatitis C Virus Infection

Since its functional characterization by Aggarwal and coworkers in 1984, TNF (all members of its superfamily included) has been implicated in no less than inflammation, apoptosis, proliferation, invasion, angiogenesis, metastasis, and morphogenesis [30]. TNFa is a cytokine that is central to the pathogenesis of inflammatory processes. The proinflammatory influence of TNFa is mediated through direct induction of other proinflammatory cytokines, metalloproteinases, and free radicals as well as through modulation of the subpopulation of regulatory T cells (Tregs) [31]. TNF was indeed originally characterized as an anticancer agent. However, most members of the TNF superfamily have both beneficial and potentially harmful effects. Cell survival, proliferative, and apoptotic signals are all activated simultaneously by TNFa and related proteins, and the balance between these signals determines whether the TNF family member induces apoptosis, proliferation, versus no effect at all. TNFa and its family members have now been linked to an array of pathophysiologies, including cancer, neurologic diseases, cardiovascular diseases, pulmonary diseases, autoimmune diseases, and metabolic diseases.

In chronic hepatitis C, inflammation is an inherent part of the disease process, and cytokines, such as TNFa, represent key regulators of the chronic inflammatory processes involved. Indeed, liver injury in HCV infection is believed to be caused by host immune responses, not by viral cytopathic effects. TNFa mediates its effects by binding to two distinct cell surface receptors, TNFR-1 and TNFR-2. Proteolytic cleavage of the extracellular parts of these receptors, in turn, releases the soluble receptors sTNFR1 (-p55) and sTNFR (-p75).

In CHC, serum levels of TNFa and both types of circulating soluble TNF receptors (sTNFR) were not only increased in infected patients compared with controls, but the levels of sTNFR correlated significantly with aminotransferase levels and the histological severity of inflammation [32].

In a study involving 1180 non-alcohol consuming patients with chronic hepatitis C related liver disease, TNFa values were found to increase significantly with the increased severity of inflammation as described by a histologic inflammatory response, regardless of the HCV genotype [33]. Reports from smaller-scale studies did not show association of TNFa levels with histology activity index in patients with CHC genotype 3 virus infections [34].

In chronic liver disease associated with HCV or other causes, hepatocyte apoptosis followed by regeneration and fibrosis is a major pathogenetic mechanism. TNFa-associated induction of cell death can be ameliorated by nuclear factor kappaB (NF-κB) activation [35]. One of the proposed mechanisms of HCV infection related liver fibrosis and impairment appears to be the enhancement of TNFa-induced apoptosis through suppression of NF-κB activation.

In studies evaluating the potential effect of various parameters on the risk for progression to hepatocellular carcinoma, among others, TNFa polymorphisms, which have been related to increase TNFa expression, were shown to be a significant factor [36-38].

TNF Inhibition in Chronic Hepatitis C Infection; Safety and Outcome

Being actively involved in the pathogenesis of a variety of human diseases, the TNF superfamily represents an active target for drug development. In the field of autoimmune diseases, agents blocking the membrane-bound TNFa, or its soluble receptors, have been shown to be efficient in RA, psoriatic arthritis, psoriasis, spondyloarthropathies, juvenile idiopathic arthritis (JIA), ulcerative colitis, and Crohn's disease. However efficient, the application of these drugs is not void of safety concerns; their use has been related to a variety of adverse reactions; side effects including, among others, serious infections, demyelinating disorders, lymphomas, solid tumors, cytopenias, and drug-induced lupus. Adverse effects compromising liver function that have been reported in the context of their use are liver toxicity (elevation of transaminases), hepatosplenic lymphomas and reactivation of hepatotropic viruses [30].

When considering the world-wide prevalence of chronic hepatitis C virus infection, the question was inevitably going to come up; is their use safe in these patients [39,40]? To date, more than 150 patients have been treated with antiTNF agents for a variety of autoimmune conditions, mainly etanercept, a monoclonal antibody targeted against the soluble receptor of TNFa, in the setting of chronic HCV infection, either as monotherapy, or in combination with adjuvant immunosuppressive treatment [41]. In the majority of the cases, liver disease in terms of viral load and transaminase levels remained stable throughout anti TNFa treatment (mean duration 11.9 months), even in the absence of previous or concomitant aetiological treatment for HCV. Transient transaminases levels' elevation was recorded in a small number of cases without a corresponding increase in the viral load; worsening of the liver condition, as defined previously, as well as improvement, respectively, was noted in a small comparable number of individuals. It is of note, however, that liver compromise was restored in the exceptional cases of liver disease progression after discontinuation of the implicated drug.

In the anecdotal cases of CHC patients under antiTNF treatment that were additionally followed up by liver biopsy, no histological progression of the liver disease was described. Experimental models have suggested a potential beneficial effect of TNF blocking agents in terms of liver histology preservation, through the promotion of hepatocyte apoptosis and the inhibition of regeneration [42].

In conclusion, even though anti-TNFa agents in the setting of concomitant HCV infection appear to be relatively safe, a definitive statement in form of treatment guidelines in analogous cases cannot be made, in the absence of long-term and large, controlled clinical trials. In cases, in which their use in patients with inflammatory diseases is justified, and clinical benefit exceeds the potential risk, close monitoring of clinical and virological data (mainly ALT and HCV viremia) is mandatory [43].

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