Interleukin-10 and chronic liver disease

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Abstract

Interleukin (IL)-10 is an important immunoregulatory cytokine produced by many cell populations. Numerous investigations suggest that IL-10 plays a major role in chronic liver diseases. IL-10 gene polymorphisms are possibly associated with liver disease susceptibility or severity. Recombinant human IL-10 has been produced and is currently tested in clinical trials. These trials may give new insights into the immunobiology of IL-10 and suggest that the IL-10/IL-10 receptor system may become a new therapeutic target.

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BIOLOGICAL CHARACTERISTICS AND REGULATION OF INTERLEUKIN-10

Interleukin-10 (IL-10) first described as a cytokine synthesis inhibitory factor for T lymphocytes produced by T helper 2 (Th2) cell clones, can inhibit interferon (IFN)-γ synthesis in Th1 cell clones[3]. The human IL-10 gene, a homodimer with a molecular mass of 37 ku, is located on chromosome 1 and encodes for 5 exons. Each monomer consists of 160 amino acids. X-ray crystal-structure-analysis showed the two identical intertwining polypeptide chains of 160 amino acids are rotated by 180° to each other, forming two domains in a V- shape structure, each containing six helices[24]. Murine and human IL-10 exhibits a homology of about 80%. Various cell populations produce IL-10 in the body, including T cell subsets (Th1, Th2, Tr1, efβ), monocytes, and macrophages. IL-10 is produced also by various cell types in other organs, including the liver[8-12]. Also, the stress axis plays a significant role in regulating IL-10 expression in vivo. Inflammation of the central nervous system or indirect activation of the stress axis by endotoxemia/bacteremia triggers the release of catecholamines that up-regulate IL-10 production in macrophages, particularly in the liver[27-8]. Within the liver, production of IL-10 has been documented within hepatocytes, sinusoidal endothelial cells, Kupffer cells, hepatic stellate cells and liver-associated lymphocytes[9]. These cells are stimulated to produce IL-10 through the cAMP/protein kinase A/CREB-1/ATF-1 signaling by several endogenous and exogenous factors such as stress, endotoxin, tumor necrosis factor-α, catecholamines, and cAMP-elevating drugs. Recent data suggest that the p38 mitogen-activated kinase pathway also regulates the human IL-10 promoter via the activation of sp1 transcription factor[14-16]. IL-10 activity is mediated by its specific cell surface receptor-IL-10 receptor, which is expressed on a variety of cells, especially in immune cells[31]. Only a few copies of IL-10R are expressed on the surface of cells[12-13]. The expression is variable, but so far only a few regulating factors are known. IL-10R is composed of two different chains[32]. The interaction of hIL-10R with hIL-10 has been characterized recently and seems to be highly complex[31-33]. The IL-10Rβchain is essential for IL-10-mediated effects and CRFB4-deficient mice display the same phenotype as IL-10 deficient mice[34]. Only in cells expressing both IL-10R α and β chains, can the characteristic pattern of IL-10 signaling be observed[35]. The IL-10/IL-10R interaction activating the tyrosine kinases Jak1 and Tyk2, inhibiting the activity of NF-κB, pathway also regulates the human IL-10 promoter via the activation of sp1 transcription factor[36]. IL-10 activity is mediated by its specific cell surface receptor-IL-10 receptor, which is expressed on a variety of cells, especially in immune cells[31]. Only a few copies of IL-10R are expressed on the surface of cells[12-13]. The expression is variable, but so far only a few regulating factors are known. IL-10R is composed of two different chains[32]. The interaction of hIL-10R with hIL-10 has been characterized recently and seems to be highly complex[31-33]. The IL-10Rβchain is essential for IL-10-mediated effects and CRFB4-deficient mice display the same phenotype as IL-10 deficient mice[34]. Only in cells expressing both IL-10R α and β chains, can the characteristic pattern of IL-10 signaling be observed[35]. The IL-10/IL-10R interaction activating the tyrosine kinases Jak1 and Tyk2, inhibiting the activity of NF-κB, results in transcriptional activation of several hundred genes[36]. The effects of IL-10 have been confirmed by experimental research in animals including IL-10 knockout mice[28] as well as by the effects of IL-10 observed in several inflammatory, autoimmune, and tumor models. IL-10 inhibits the ability of monocytes and macrophages to produce antigens to T cells[21-22] and monocyte production of IL-12. Inhibits proliferation and cytokine synthesis of CD4+ T cells by exerting some direct effects of T cells, but does not exert potent direct inhibitory effects on CD8+ T cells. IL-10 has various but weak stimulatory effects on B cells. IL-10 prevents apoptosis and enhances proliferation and differentiation of plasma cells as well as IgM synthesis, and inhibits the release of various chemokines by neutrophils. One of the most important properties of IL-10 is its anti-inflammatory action[25], which restrains the
immune response under various stimuli. Evidence of in vivo function of IL-10 indicates that inflammatory bowel disease is exacerbated in the absence of IL-10.

**EFFECTS OF IL-10 ON CHRONIC LIVER DISEASE AND LIVER FIBROSIS**

Experimental data from animal models and clinical data from patients suggest that inflammation-associated cytokines including pro-inflammatory cytokines such as TNF-z and TGF-β, and anti-inflammatory cytokines such as IL-10, are involved in the development of liver injury. The effects of IL-10 have been observed in viral or autoimmune hepatitis, alcoholic liver disease, and animal models. Patients with a strong Th1 response during acute HCV infection can clear the virus, while patients presenting with a Th2 response (high levels of IL-10) evolve into chronicity. In Con A-induced liver injury model, using a blocking IL-10 monoclonal antibody could lead to severe hepatic necrosis. On the other hand, administration of recombinant IL-10 in mice challenged with Con A could dramatically reduce secretion of pro-inflammatory cytokines, apoptosis of hepatocytes, hepatic neutrophil infiltrate and delay hepatic necrosis. In the model of liver injury induced by lipopolysaccharide (LPS) or staphylococcal enterotoxin B (SEB) in D-galactosamine (Galan)-sensitized mice, treatment with IL-10 could markedly reduce serum transaminase activities in a dose-dependent manner and hemorrhagic liver damage in sensitized mice exposed to toxins. IL-10 also inhibits increases in serum TNF-alpha and IFN-gamma concentrations with the toxins. Treatment with IL-10 could significantly reduce TNF-alpha mRNA and IFN-gamma mRNA expression in the liver and spleen after administration of the toxins to sensitized mice. These findings suggest that IL-10 is capable of regulating hepatic injury in vivo mediated by T cells macrophages. Injury of the liver requires the participation of proinflammatory cytokines and chemokines, many of which are regulated by the transcription factor, nuclear factor xB (NFxB). Other data suggest that IL-10 protects against hepatic ischemia/reperfusion injury by suppressing NFxB activation and subsequent expression of proinflammatory mediators. IL-10 has been shown to be beneficial in the setting of liver transplantation, treatment with IL-10 can increase allograft survival. Current studies demonstrate that IL-10 may protect against surgery- or trauma related organ injuries secondary to hepatic ischemia-reperfusion. In human alcoholic liver disease or in rats fed with alcohol, defective production of IL-10 might result in chronic liver disease, suggesting that IL-10 might be of therapeutic value for alcoholic hepatitis by decreasing hepatocyte death. In the model of CCI4-induced chronic liver injury, IL-10 deficient animals had a persistently increased inflammatory infiltrate, and developed more extensive fibrosis than the animals able to produce IL-10, indicating that IL-10 is involved in the control of fibrogenesis. Several studies indicate that IL-10 might play an important role in antifibrogenesis during CCl4-induced hepatic fibrogenesis. Hepatic stellate cells (HSCs) are involved in liver fibrogenesis since, in vitro experiments have shown that HSCs express IL-10 receptor and produce IL-10. In highly purified preparations of rat HSCs, messenger RNA (mRNA) for IL-10 can be detected by reverse-transcription polymerase chain reaction (RT-PCR). Long-term incubation of unstimulated mouse HSCs secretes IL-10 protein as detected by immunoblotting and specific enzyme-linked immunosorbent assay (ELISA). IL-10 protein is undetectable by immunohistochemistry in mouse HSCs during the first 3 d of culture. The percentage of IL-10-positive cells increases to 45% on d 7 and 100% on d 14, and IL-10 continues its expression in long-term culture of up to 120 d. These data indicate that IL-10 plays an important role in liver fibrosis by suppressing the function of HSC and promoting apoptosis of HSC.

**IL-10 GENE POLYMORPHISMS IN CHRONIC LIVER DISEASE**

Genetic markers in cytokine genes are widely used in studies of immune-mediated diseases to determine disease susceptibility and severity. In recent years, increasing attention has been paid to the role of cytokine levels in inflammatory and immune response, which may account for some of the heterogeneity observed in the outcome of chronic liver diseases, such as HBV and HCV infection, alcoholic and autoimmune hepatitis. Possible linkage of IL-10 promoter haplotypes to disease susceptibility or severity has been reported. The IL-10 promoter is highly polymorphic with two informative microsatellites, IL-10G and IL-10R. Single nucleotide polymorphisms (SNPs) in the promoter form SNP combinations (ATA, ACC, GCC) associated with differential IL-10 expression. There are several lines of evidence that ATA haplotype in the IL-10 gene promoter is relevant to a genetically low capacity for IL-10 production, whereas GCC haplotype is identified as a high IL-10-producing phenotype, suggesting that the difference in disease progression of patients results from the inheritance of the IL-10 gene promoter polymorphisms. The influence of cytokine genotypes either on different clinical features of liver disease or in the response to antiviral therapy has been evaluated in several studies. Since inadequate expression of IL-10 seems to be of physiopathological relevance in several diseases and the expression levels seem to have a genetic background. Increased serum levels of IL-10 are often observed in chronic HCV infection and inheritance of the interleukin-10 -1082 G/G may be associated with susceptibility to chronic hepatitis C infection and resistance to combined antiviral therapy, suggesting that chronic HCV infection patients with the haplotype conferring a high production of IL-10 have a lower rate of response to interferon therapy. IL-10 promoter allelic frequencies of T and A at positions -819 and -592, as well as the frequencies of ATA haplotype at positions -1082/ -819/ -592, are significantly higher in asymptomatic carriers than in patients with progressive chronic liver disease, suggesting that patients with haplotype
confering a high production of IL-10 develop chronic progressive liver disease, while patients with a lower production of IL-10 tend to be asymptomatic carriers. Possession of the A allele at position -627 in the IL-10 promoter (low IL-10 expression) is associated with an increased risk of advanced liver disease in heavy drinkers.

Genetic association analysis has revealed that one of the IL-10 haplotypes, IL-10-hs (-1082A/-819T/-592C/+117T) is strongly associated with hepatocellular carcinoma (HCC) occurrence in a dose-dependent manner. The frequency of susceptible IL-10-hs is much higher in HCC patients and significantly increased in order of susceptibility to HBV progression from chronic to cirrhosis and HCC. In addition, the onset age of HCC is also accelerated among chronic hepatitis B patients who carry IL-10-hs. Increased IL-10 production mediated by IL-10-hs suggests that up-regulation of IL-10 accelerates progression of chronic HBV infection, to HCC.

APPLICATION OF IL-10 AS A THERAPEUTIC AGENT

The promising results from IL-10 applied to several inflammatory diseases in experimental models induce the interest in clinical application of IL-10. So far human recombinant IL-10 has been tested in healthy volunteers, patients with Crohn's disease, rheumatoid arthritis, psoriasis, hepatitis C and HIV infection. In phase I clinical trials, safety, tolerance, pharmacokinetics, pharmacodynamics, immunological and hematological effects of single or multiple doses of IL-10 administered by intravenous (i.v.) or subcutaneous (s.c.) route have been investigated in healthy volunteers. IL-10 is well tolerated without serious side effects at the dose of 25 μg/kg and mild to moderate flu-like symptoms are observed in a fraction of recipients at the doses of 100 μg/kg.

Single i.v. or s.c. of IL-10 results in transient dose-dependent changes in white blood cell population, including increase of total white blood cells and neutrophils, lymphocytopenia and monocytes as well as decrease in platelet counts are observed. Following i.v. administration, IL-10 serum levels initially decline rapidly but yields a less steep terminal phase. IL-10 is cleared mainly through the kidneys as indicated by the increased t1/2 and AUC of IL-10 in patients with moderate to severe renal insufficiency. Taken together, IL-10 application induces a number of immunological changes and is well tolerated. IL-10 treatment does not result in significantly higher remission rate or clinical improvement for Crohn's disease compared with placebo treatment. IL-10 can prevent postoperative recurrence of Chorine's disease but the clinical results are unsatisfactory. The data from rheumatoid arthritis patients are rather discouraging, showing only marginal activity of the drug. For psoriasis, IL-10 is likely to have antipsoriatic activity.

IL-10 is able to express antifibrotic properties in experimental models of liver cirrhosis. It has been postulated that in vivo administration of IL-10 to patients with HCV infection may shift the intrahepatic immunologic balance away from Th1 cytokine predominance, thus exerting its anti-inflammatory and subsequent antifibrotic effect. It was reported that long-term therapy with interleukin-10 decreases hepatic inflammatory activity and fibrosis, but leads to increased HCV viral levels.

IL-10 increases the susceptibility to infections due to its immunosuppressive activity and inhibition of bactericidal activity. In the future, it may be used to target the delivery of IL-10 to avoid systemic side effects and low biodisponibility. IL-10 could be delivered locally with an adenosine virus in the liver, suggesting that anti-inflammatory cytokines may have a future in the treatment of liver injury and the prevention of its complications.

REFERENCES

1. Fiorentino DF, Bond MW, Mosmann TR. Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. J Exp Med 1989; 170: 2081-2095
2. Moore KW, de Waal Malefyt R, Coffman RL, O’Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 2001; 19: 683-765
3. Zdanov A, Schalk-Hihi C, Gutchina A, Tsang M, Weatherbee J, Wlodawer A. Crystal structure of interleukin-10 reveals the functional dimer with an unexpected topological similarity to interferon gamma. Structure 1995; 3: 591-601
4. Spits H, de Waal Malefyt R. Functional characterization of human IL-10. Int Arch Allergy Immunol 1992; 99: 8-15
5. Platzer C, Doeke W, Volk H, Prosch S. Catecholamines trigger IL-10 release in acute systemic stress reaction by direct stimulation of its promoter/enhancer activity in monocytytic cells. J Neuroimmunol 2000; 105: 31-38
6. Riese U, Brenner S, Doeke WD, Prosch S, Reinke P, Oppert M, Volk HD, Platzer C. Catecholamines induce IL-10 release in patients suffering from acute myocardial infarction by transactivating its promoter in monocytic but not in T-cells. Mol Cell Biochem 2000; 212: 45-50
7. Jilg S, Barsig J, Leist M, Kusters S, Volk HD, Wendel A. Enhanced release of interleukin-10 and soluble tumor necrosis factor receptors as novel principles of methylxanthine action in murine models of endotoxic shock. J Pharmacol Exp Ther 1996; 278: 421-431
8. Wiociechowsky C, Asadullah K, Nestler D, Eberhardt B, Platzer C, Schoning B, Glöckner F, Lanksch WR, Volk HD, Doeke WD. Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury, Nat Med 1998; 4: 808-813
9. Wan S, LeClerc JL, Schmartz D, Barvais L, Huyenh CH, Deviere J, DeMets JM, Vincent JL. Hepatic release of interleukin-10 during cardiopulmonary bypass in steroid-pretreated patients. Am Heart J 1997; 133: 335-339
10. Ma W, Lim W, Gee K, Aucoin S, Nandan D, Kozlowski M, Diaz-Mitoma F, Kumar A. The p38 mitogen-activated kinase pathway regulates the human interleukin-10 promoter via the activation of Sp1 transcription factor in lipopolysaccharide-stimulated human macrophages. J Biol Chem 2001; 276: 13664-13674
11. Dumoutier L, Renaud JC. Viral and cellular interleukin-10 (IL-10)-related cytokines: from structures to functions. Eur Cytokine Netw 2002; 13: 5-15
12. Carson WE, Lindemann MJ, Baiocchi R, Linett M, Tan JC, Chou CC, Narula S, Caligiuri MA. The functional characterization of interleukin-10 receptor expression on human natural killer cells. Blood 1995; 85: 3577-3585
13. Jurlander J, Lai CF, Tan J, Chou CC, Geisler CH, Schrier J, Blumenson LE, Narula SK, Baumann H, Caligiuri MA. Characterization of interleukin-10 receptor expression on human natural killer cells. J Exp Med 1997; 185: 4146-4152
14. Donnelly RP, Sheikh F, Kotenko SV, Dickensheets H. The expanded family of class II cytokines that share the IL-10-1 receptor-2 (IL-10R2) chain. J Leukoc Biol 2004; 76: 314-321
15. Reineke U, Sabat R, Volk HD, Schneider-Mergener J. Map...
ping of the interleukin-10/interleukin-10 receptor combining site. Protein Sci 1998; 7: 951-960

Reineke U, Schneider-Mergener J, Glaser RW, Stigler RD, Seifert M, Volkt HD, Sabat R. Evidence for conformationally different states of interleukin-10: binding of a neutralizing antibody enhances accessibility of a hidden epitope. J Mol Recognit 1999; 12: 242-248

Spencer SD, Di Marco F, Hooley J, Pitts-Meek S, Bauer M, Ryan AM, Sordat B, Gibbs VC, Aguet M. The orphan receptor CRF2-4 is an essential subunit of the interleukin 10 receptor. J Exp Med 1998; 187: 571-578

Kotenko SV, Krause CD, Izotova LS, Pollack BP, Wu W, Pestka S. Identification and functional characterization of a second chain of the interleukin-10 receptor complex. EMBO J 1997; 16: 5894-5903

Clarke CJ, Hales A, Hunt A, Foxwell BM. IL-10-mediated suppression of TNF-alpha production is independent of its ability to inhibit NF kappa B activity. Eur J Immunol 1998; 28: 1719-1726

Rennick D, Davidson N, Berg D. Interleukin-10 gene knockout mice: a model of chronic inflammation. Clin Immunol Immunopathol 1995; 76: S174-S178

Grutz G. New insights into the mechanism of interleukin-10-mediated immunosuppression. J Leukoc Biol 2005; 77: 3-15

Yue FY, Dummer R, Geertsens R, Hofbauer G, Laine E, Manolio S, Burg G. Interleukin-10 is a growth factor for human melanoma cells and down-regulates HLA class-I, HLA class-II and ICAM-1 molecules. Int J Cancer 1997; 71: 630-637

Dokka S, Shi X, Leonard S, Wang L, Castranova V, Rojana-sakul Y. Interleukin-10-mediated inhibition of free radical generation in macrophages. Am J Physiol Lung Cell Mol Physiol 2001; 280: L1196-L1202

Knolle PA, Gerken G. Local control of the immune response in the liver. Immunol Rev 2000; 174: 21-34

Barrat FJ, Cua DJ, Boonstra A, Richards DF, Crain C, Savelkoul HF, de Waal-Malherbe K. Cytokine gene polymorphism in humans. Immunol Cell Biol 1997; 75: 187-217

Louis H, Le Moine A, Quertinmont E, Peny MO, Geerts A, Goldman M, Le Moine O, Winkel J, Pabst M, Kato A, Edwards MJ, Lentsch AB. Interleukin-10 inhibits hepatic injury and tumor necrosis factor-alpha and interferon-gamma mRNA expression in chronic hepatitis C. J Hepatol 1998; 28: 397-416

Thompson KC, Malthy J, Fallowfield J, McAuley M, Millward-Sadler H, Sheron N. Interleukin-10 expression and function in experimental murine liver inflammation and fibrosis. Hepatol 1998; 28: 1597-1606

Zhang LJ, Yu JP, Di L, Huang YH, Chen ZX, Wang XZ. Effects of cytokines on carbon tetrachloride-induced hepatic fibrogenesis in rats. World J Gastroenterol 2004; 10: 77-81

Wang XZ, Chen ZX, Zhang LJ, Chen YX, Li D, Chen FL, Huang YH. Expression of insulin-like growth factor I and insulin-like growth factor I receptor and its intervention by interleukin-10 in experimental hepatic fibrosis. World J Gastroenterol 2003; 9: 1287-1291

Wang XZ, Zhang LJ, Di L, Huang YH, Chen ZX, Li B. Effects of transmitters and interleukin-10 on rat hepatic fibrosis induced by CCl4. World J Gastroenterol 2003; 9: 539-543

Wang SC, Ohta M, Schum L, Rippe RA, Takaisho H. Expression of interleukin-10 by in vivo and in vitro activated hepatic stellate cells. J Biol Chem 1998; 273: 302-308

Mathurin P, Xiong S, Kharbanda KK, Veal N, Miyahara T, Tomomura K, Rippe RA, Bachem MG, Takaisho H. IL-10 receptor and coreceptor expression in quiescent and activated hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2002; 282: G981-G990

Pinzani M, Marra F. Cytokine receptors and signaling in hepatic stellate cells. Semin Liver Dis 2001; 21: 397-416

Thompson KC, Trowell A, Fowell A, Marathe M, Haycock C, Arthur MJ, Sheron N. Primary rat and mouse hepatic stellate cells express the macrophage inhibitor cytokine interleukin-10 during the course of activation In vitro. Hepatology 1998; 28: 1518-1524

Wang XZ, Zhang SJ, Chen YX, Chen ZX, Huang YH, Zhang LJ. Effects of platelet-derived growth factor and interleukin-10 on Fas/Fas-ligand and Bel-2/Bax mRNA expression in rat hepatic stellate cells in vitro. World J Gastroenterol 2004; 10: 2706-2710

Zhang LJ, Chen YX, Chen ZX, Huang YH, Yu JP, Wang XZ. Effect of interleukin-10 and platelet-derived growth factor on expressions of matrix metalloproteinases-2 and -9. Inhibition of metalloproteinases-1 in rat fibrotic liver and cultured hepatic stellate cells. World J Gastroenterol 2004; 10: 2574-2579

Reitamo S, Remitz A, Tamaki K, Uitto J. Interleukin-10 modulates type I collagen and matrix metalloproteinase gene expression in cultured human skin fibroblasts. J Clin Invest 1994; 94: 2489-2492

Louis H, Le Moine O, Goldman M, Deviere J. Modulation of liver injury by interleukin-10. Acta Gastroenterol Belg 2003; 66: 7-14

Biddwell J, Keen L, Gallagher G, Kimberly R, Huizinga T, Mcderr-mott MF, Oksenberg J, McNicholl J, Pocic F, Hardt C, D’Alfonso S. Cytokine gene polymorphism in human disease: on-line databases. Genes Immun 1999; 1: 3-19

Kingo K, Koks S, Sihm H, Varas E. IL-10 promoter polymorphisms influence disease severity and course in psoriasis. Genes Immun 2003; 4: 455-457

Eskdale J, Keijser S, Huizinga T, Gallagher G. Microrna-satellite alleles and single nucleotide polymorphisms (SNP) combine to form four major haplotype families at the human interleukin-10 (IL-10) locus. Genes Immun 1999; 1: 151-155

Vidigal PG, Germer JI, Zien NN. Polymorphisms in the interleukin-10, tumor necrosis factor-alpha, and transforming growth factor- betal genes in chronic hepatitis C patients treated with interferon and ribavirin. J Hepatol 2002; 36: 271-277

Yee LJ, Tang J, Gibbons R, Kinney R, Van Leeuwen DJ, Kaslow RA. Interleukin 10 polymorphisms as predictors of sustained re- sponse in antiviral therapy for chronic hepatitis C infection. Hepatol

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www.wjgnet.com
Mangia A, Santoro R, Piattelli M, Pazienza V, Grifa G, Iacobellis A, Andruilli A. IL-10 haplotypes as possible predictors of spontaneous clearance of HCV infection. Cytokine 2004; 25: 103-109

Miyazoe S, Hamasaki K, Nakata K, Kajiya Y, Kitajima K, Nakao K, Daikoku M, Yatsuhashi H, Koga M, Yano M, Eguchi K. Influence of interleukin-10 gene promoter polymorphisms on disease progression in patients chronically infected with hepatitis B virus. Am J Gastroenterol 2002; 97: 2086-2092

Wang FS. Current status and prospects of studies on human genetic alleles associated with hepatitis B virus infection. World J Gastroenterol 2003; 9: 641-644

Grove J, Daly AK, Bassendine MF, Gilvarry E, Day CP. Interleukin 10 promoter region polymorphisms and susceptibility to advanced alcoholic liver disease. Gut 2000; 46: 540-545

Song Z, Joshi-Barve S, Barve S, McClain CJ. Advances in alcoholic liver disease. Curr Gastroenterol Rep 2004; 6: 71-76

Shin HD, Park BL, Kim LH, Jung JH, Kim YJ, Yoon JH, Kim YJ, Lee HS. Interleukin 10 haplotype associated with increased risk of hepatocellular carcinoma. Hum Mol Genet 2003; 12: 901-906

Boyer N, Marcellin P. Pathogenesis, diagnosis and management of hepatitis C. J Hepatol 2000; 32: 98-112

Huhn RD, Ladwanski E, Gallo J, Affrime MB, Sabo R, Gonyo G, Monge A, Cutler DL. Pharmacodynamics of subcutaneous recombinant human interleukin-10 in healthy volunteers. Clin Pharmacol Ther 1997; 62: 171-180

Huhn RD, Pennline K, Ladwanski E, Clarke L, Sabo R, Cutler DL. Effects of single intravenous doses of recombinant human interleukin-10 on subsets of circulating leukocytes in humans. Immunopharmacology 1999; 41: 109-117

Ilan Y. Oral tolerance: a new tool for the treatment of gastrointestinal inflammatory disorders and liver-directed gene therapy. Can J Gastroenterol 1999; 13: 829-835

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

Colombel JF, Rutgeerts P, Malchow H, Jacyna M, Nielsen OH, Rask-Madsen J, Van Deventer S, Ferguson A, Desreumaux P, Forbes A, Geboes K, Melani L, Cohard M. Interleukin 10 (TeNovil) in the prevention of postoperative recurrence of Crohn’s disease. Gut 2001; 49: 42-46

Keystone E, Wherry J, Grint P. IL-10 as a therapeutic strategy in the treatment of rheumatoid arthritis. Rheum Dis Clin North Am 1998; 24: 629-639

Friedrich M, Dockey WD, Klein A, Philipp S, Volk HD, Sterry W, Asadullah K. Immunomodulation by interleukin-10 therapy decreases the incidence of relapse and prolongs the relapse-free interval in Psoriasis. J Invest Dermatol 2002; 118: 672-677

Nelson DR, Lauwers GY, Lau JY, Davis GL. Interleukin 10 treatment reduces fibrosis in patients with chronic hepatitis C: a pilot trial of interferon nonresponders. Gastroenterology 2000; 118: 655–660

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

Kalechman Y, Gafter U, Gal R, Rushkin G, Yan D, Albeck M, Sredni B. Anti-IL-10 therapeutic strategy using the immunomodulator AS101 in protecting mice from sepsis-induced death: dependence on timing of immunomodulating intervention. J Immunol 2002; 169: 384-392

Quattrocchi E, Dallman MJ, Dhillon AP, Quaglia A, Bagnato G, Feldmann M. Murine IL-10 gene transfer inhibits established collagen-induced arthritis and reduces adenosine-mediated inflammatory responses in mouse liver. J Immunol 2001; 166: 5970-5978