CHALLENGES AND SOLUTIONS IN TODAY'S INTERNAL MEDICINE

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December 2014

In the vast field of internal medicine there are numerous debates, which constitute at the same time challenges, related to pathophysiological mechanisms, diagnosis and treatment of different diseases, which require to elaborate solutions, which will be reflected finaly in the improvement of therapeutic results.

In the field of physiopathology we carry out studies on the role of cytokines and erythropoietin in chronic liver diseases. It is known that in addition to antiapoptotic and proangiogenic effect, erythropoietin can inhibit serum level of IL-6 and TNF-alpha, at systemic and paracrine level, but its effects on liver have been less studied. Dosing the proinflammatory cytokines and erythropoietin to a group of 96 patients we found that those chronic infected with hepatitis C virus have significantly higher levels of IL-6, IL-8 and larger, but nonsignificant, of TNF-alpha compared with those noninfected. The levels of serum erythropoietin were also significantly higher in those infected with hepatitis C virus compared to healthly subjects, growth which could be reactive to the liver inflammatory process. It may be speculate that in the absence serum erythropoietin levels increase, the serum levels of liver proinflammatory cytokines would have been higher. The fact that the 3 liver proinflammatory cytokines have significantly higher serum levels and erythropoietin levels were significantly lower in patients chronicly infected with hepatitis C virus and chronic renal failure, found in a program of chronic hemodialysis, compared to the patients chronicly infected with hepatitis C virus and without renal failure, may plead for a possible anti-inflammatory effect of erythropoietin, outside of its drop due to the chronic renal failure (although patients received replacement treatment with 5,000 IU of recombinant erythropoietin-alpha per week). In another study that included 78 hospitalized patients, serum level of erythropoietin was significantly higher in patients with nonalcoholic steatosis and steatohepatitis, comparing to the healthy witness, while serum levels of IL-6 and TNF-alpha of those with liver steatosis, but not of those with nonalcoholic steatohepatitis, have been significantly higher than those of the witnesses. Our findings suggest a possible anti-inflammatory effect of erythropoietin in nonalcoholic steatohepatitis.

The treatment of chronic liver diseases was another objective of my researches. In a multicenter randomized trial that included 87 patients with nonalcoholic steatohepatitis, we found that to the dyslipidemic group, treated with lovastatin, the transaminases and cholesterolemia decreased significantly after one month and after 2 months, and APRI score (which assesses noninvasively liver fibrosis) - after 2 months of treatment. The group without dyslipidemia, treated with pentoxyphyllin, transaminases decreased significantly after a month, and Forns index - after 2 months of treatment. The decrease of noninvasive markers of liver fibrosis in patients with nonalcoholic steatohepatitis under treatment with lovastatin or pentoxyphylline is a reason not only for beneficial pleiotropic effects of these drugs on liver biochemical tests, but also on liver histology, an important finding due to the fact that most patients have refused the proposal of first liver biopsy, and so much more of the second (for the study of the liver architecture dynamics). Statins inhibit not only the cholesterol synthesis, but also the processes of geranyl-geranylation.

Experimental studies have suggested that a geranyl-geranylated protein is involved in hepatitis C virus replication. In a multicenter randomized trial that included 101 patients, we found that 58,54 % of those with chronic hepatitis C, who had completed the therapy with pegylated interferon and ribavirin, and who had liver cytolysis and RNA of hepatitis C virus present in the blood at the inclusion in the study presented significant decrease of viremia after 3 months of

treatment with simvastatin 20 mg/day. In addition, it was also shown a significantly decrease of cholesterolemia and serum alkaline phosphatase after one month and 2 months of treatment with simvastatin. The statin was, generally, well tolerated, without major adverse effects. In another multicenter randomized trial that included 99 patients with chronic hepatitis C who had detectable viremia, this has dropped to 63.64% of them after 4 weeks of treatment with lovastatin (20 mg/day) or fluvastatin (40 mg/day). To the entire group of patients, the decrease has been statistically significant. In addition, lovastatin has produced a significant decrease of serum levels of IL-6 and TNF-alpha, and fluvastatin of those of IL-6, IL-8 and TNF-alpha, which has been more important than the one produced by lovastatin. On the other hand, the significant decrease of serum levels of direct bilirubin and alkaline phosphatase after 4 weeks of therapy with lovastatin advocates for an anticholestatic effect of this statin.

Our research on the pleiotropic effects of statins in chronic hepatitis C have been pursued by various researchers from all over the world and have been published by me in a literature review, of which we mention the results of a Japanese team, who has associated to pegylated interferon and ribavirin pitavastatin and eicosapentaenoic acid (which can suppress the expression of low-density lipoprotein receptor which is required for hepatitis C virus entry in hepatocyte), and which has resulted in a higher rate of sustained virological response comparing with the standard therapy.

Another objective of my researches is the study of thrombotic risk in chronic liver diseases. In a multicenter observational study that included 215 patients with hepatocellular carcinoma, we found out that more than a third of the patients had venous thrombosis in the past or at the time of study. The most common location was portal. The thrombotic risk was not correlated with the mean platelet volume or other platelet indices, but it has been correlated directly with the number of platelets. The thrombotic events were not correlated with the thrombotic risk score (proposed by Khorana AA et al) or with the platelet indices. The small number of megakaryocytes and the low level of thrombopoietin explain this lack of correlation. The dysfunctions of coagulation, fibrinolysis and hemostasis processes and the direct tumoral effects are involved in the thrombotic events of these patients and can aggravate the disease evolution and, sometimes, establish the prognosis. Therefore, their prophylaxis must be taken into account in each case and its opportunity must be analyzed dependent on individual particularities and risks.

We also analyzed the thrombotic risk in patients with primary immune thrombocytopenia. In a pilot study, we found that they had a peak of thrombin generation significantly higher than the health witnesses. The lower the age of patients with primary immune thrombocytopenia, the higher the peak of thrombin generation. The smaller the platelet count in patients with primary immune thrombocytopenia, the higher the peak of thrombin generation – one of the reasons which explains why their bleeding accidents are rare.

In this thesis, there are also references to the literature review developed by me, on the usefulness of thrombopoietin receptor analogues in chronic hepatitis C, cholesterol and triglycerides metabolism disorders in malignant hemopathies, the adjuvant role of statins in the treatment of malignant hemopathies and an attempt to answer the question if resveratrol could be a useful drug for the same category of diseases. The thesis also contains some presentations of rare cases, of serious associated diseases or with particular evolution, which constitute another constant of my concerns.