DIAGNOSTIC AND TREATMENT OF CHRONIC HCV INFECTION IN BULGARIA – PAST AND PRESENT

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Abstract

HCV infection is one of the most important challenges of the health care system in East Europe. Efforts in improving the diagnosis and the therapy of this disease have been done in recent years in our country.

This paper reports our national experience in detecting HCV infection and fighting its consequences. Our strategy is based on international consensus. This review shows also the steps done in increasing the accuracy of diagnosis and improving therapy.

Keywords: chronic hepatitis, HCV infection, interferon.

DIAGNOSTICUL ŞI TRATAMENTUL INFECŢIEI CRONICE CU VHC ÎN BULGARIA

Rezumat

Infecţia cu VHC este una dintre cele mai mari provocări ale sistemului sanitar din ţările est-europene. Eforturi de a ameliora diagnosticul şi terapia acestei boli au fost realizate în ultimii ani în ţara noastră. Strategia noastră este bazată pe consensuri internaţionale. Acest referat prezintă paşii efectuaţi în îmbunătăţirea acurateţii diagnostice şi în îmbunătăţirea terapiei.

Cuvinte cheie: hepatită cronică, infecţie cu VHC, interferon.

The diagnostic and treatment of chronic hepatitis C have long story in Bulgaria such others countries in the world. Officially it started with discovery of HCV in 1989. But many years ago the diagnose NonA NonB hepatitis was used for designation of hepatitis born manly after blood transfusion and there were some attempts to treat these patients with antioxidants.

The first commercial available ELISE kits for detection of anti-HCV antibodies were introduced in Bulgaria in 1990. Using such kits the frequency of 1.1% anti-HCV (+) carriers was found among Bulgarian blood donors. We discovered that 52% of patients with porphyria cutanea tarda and 75% of patients with haemophilia were anti-HCV (+) positive [1]. Elevated ALT plus positive anti-HCV antibodies, absent of HBsAg, autoantibodies and alcohol abuse ware enough for diagnosis of chronic hepatitis C. The method for detection of HCV RNA was not available in Bulgaria at this time.

The first antiviral drugs used by us for treatment of chronic HCV infection was lymfoblastoid interferon alfa [2] and recombinant interferon alfa [3] in doses 3 ME s.c. three times weekly for 6 months. The results from such treatment were too disappointed. There were no patients with normal ALT during the follow up after the stopping of therapy.

HCV RNA was proven by commercial PCR – Amplicor (Roche) for the first time in the spring of 1994. Using Amplicor we founded that about 29% of anti-HCV positive blood donors actually did not have HCV RNA. All HCV RNA negative patients had normal ALT and majority of them were former drug abusers. We did not founded HCV RNA positive but anti-HCV negative patients with acute post transfusion hepatitis.

A year later, in 1995 a commercial quantitative PCR (Monitor) was available. This let us to follow up the changes in HCV RNA levels during the interferon alfa treatment. A big issue it was the necessary to dilute the samples to get correct results if HCV RNA was more than 100 000 copies/ ml.

To avoid this new bDNA method was implemented for diagnostic of HCV RNA in 1995. With bDNA one measurement of HCV RNA was enough to get correct results. But the sensitivity of bDNA was lower than PCR

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– Amplicor. Both methods were necessary to follow up the changes in HCV RNA caused by interferon alfa treatment - bDNA or PCR-Monitor before and during the treatment and PCR Amplicor – at the end of the treatment and at the end of 6 months follow up [4].

New moment in the diagnostic of chronic HCV infection was the finding that HCV genotypes were clinically significant. HCV genotypes responded differently on interferon alfa treatment. HCV genotypes 2 and 3 responded better than HCV genotype 1 or 4. Serological genotyping of HCV was implemented in Bulgaria for the first time in 1996 [5]. It was founded that HCV genotype 1 was most common infection in Bulgarian patients – near 82%. About 12% of patients were infected with HCV genotype 3 and 4% had mix infection – genotype 1 with genotype 2 or genotype 3. The percent of "ungenotyping" patients with first serological genotyping kits was too high – more than 30 %. We founded the reason for that was anti-HCV antibodies profile [6]. The patients with low level antibodies against Cor and NS3/NS4 proteins of HCV were "ungenotyping". With second generation of serological HCV genotyping the situation was much more improved. The percent of "ungenotyping" patients dropped to less than 10%.

The breakthrough in treatment of chronic HCV infection happened in 1996-1997 with introduction of combined treatment interferon alfa 2b and ribavirin for 6 months and for 12 months. Our result showed 36% and 54% sustained viriogycal response in the first case and in the second case [7]. The number of treated patient gradually increased. This combined treatment became part of National held program.

At the end of XX century the diagnostic of HCV infection improved with implementation of COBAS Amplicor – automatic PCR. With this PCR was reached standardization of the assay and comparison of the results.

Serological HCV genotyping was replace with VERSANT HCV genotyping LIPA assay with opportunity to show and subgroups of HCV genotypes. The prevalence of different HCV genotypes investigated with VERSANT was the same such previously founded – 88% HCV genotype 1 and majority of them subgroup "b", 10% HCV genotype 3. There were no differences in percent of mix infections investigated with both methods.

The "Golden Age" of HCV infection treatment became with introducing combination of PEG-Interferons and ribavirin. Now the Standard of Care (SOC) in Bulgaria is combined therapy PEGASYS 180 µg or PegIntron 1,5 µg/kg / week s.c. plus ribavirin (COPEGUS; Rebetol) 1000-1200 mg/ day p.o. for 12 months duration in cases with HCV genotype 1 infection and for 6 months in cases with HCV genotype 2 and 3 infections. The Sustained Viriogical Response (SVR) reached 81% in our group treated patients [8]. They were good selected patients – younger and with lower percent of liver cirrhosis compared with the patients in first published clinical trials.

Since 2005 the real time PCR (RT-PCR) became the base assay in Bulgaria for measuring of serum HCV RNA. The main reason was the good linearity of the assay – from 50 IU/ml to the 100 000 000 IU/ml. RT-PCR replaced and both assays - COBAS Amplicor and bDNA.

Now the agenda of chronic HCV infection treatment is to individualize the therapy according viriogical response. The duration of therapy have to be depending of the time when HCV RNA becomes undetectable in patient's blood.

Patients nonresponders or with relapse after first course of interferon treatment received the second therapy with PEG-interferon and ribavirin. The number of these patients is still small and the efficacy of re-treatment is not clear.

We investigated how others factors different from viral can influents on interferon treatment response. We proved that SVR is with 27% less in patients with liver steatosis compared with SVR in patients without liver steatosis [9]. We found that thyroid dysfunction was very often in patients with HCV infection before and during the interferon treatment [10]. These finding often made treatment not possible. In patient not suitable for interferon treatment and with high blood level of Fe periodic phlebotomy was introduced. In result long lasting normalization of ALT was found in 82% of patient [11].

There are many clinical centers in Bulgaria, predominantly in University hospital, which participate in large number international clinical studies for treatment of chronic HCV infection. This allows us to have experience with new kind of ribavirin, therapeutic vaccines, new interferons, protease and polymerase inhibitors before their registration.

In conclusion the future of HCV infection treatment looks very promising and we are going to do everything to realize it.

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