INTERVIEW

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Screening and treatment of hepatitis B virus to prevent liver cancer in Africa

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Q Dr Thursz, can you tell us a little about your professional background to date?

I initially trained in internal medicine and gastroenterology. I was given the opportunity to train in Hepatology at St Mary's Hospital in 1990 by Prof Howard Thomas, who at that time was very active in the field of viral hepatitis and had also set up a liver transplant program. I undertook research at St Mary's Hospital Medical School which subsequently became Imperial College between 1991 and 1994 studying immunogenetics of hepatitis B virus infection. I was fortunate enough to collaborate with Prof Adrian Hill from Oxford, which resulted in a number of high-impact publications on genetic susceptibility in hepatitis B virus infection [1–4]. I became lecturer and then senior lecturer at Imperial, working mostly on genetic susceptibility in viral hepatitis but also studying the natural history of hepatitis C virus infection. In 2002, I became secretary of the British Association for Study of the Liver, a position I held for 3 years. On the retirement of Prof Thomas in 2011, I was appointed head of the Section of Hepatology and Gastroenterology at Imperial College. In 2009, I was elected to the Governing Board

of the European Association for Study of the Liver (EASL) as Vice-Secretary, and from 2011 to 2013 I served as Secretary-General of EASL. My department is involved in a wide range of basic, translational and clinical research in liver disease. We have participated in many of the recent Phase II and III trials of direct acting antivirals for hepatitis C virus infection. I have just completed a large trial of treatment for alcoholic hepatitis evaluating the role of steroids and pentoxifylline.

Q How did you come to be involved in studies into cirrhosis, hepatitis B virus & hepatocellular carcinoma? What first interested you in this area?

When I first began research on hepatitis B virus (HBV) infection, I worked on samples from patients based in Gambia, West Africa. At that time there were no effective treatments for HBV so it was ethically acceptable to study the natural history and the effect of genetic variables on the progression of disease. Many of my collaborations involved Prof Andrew Hall at the London School of Hygiene and Tropical Medicine and Prof Hilton Whittle at the MRC Laboratories in Gambia. They had been studying the

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natural history of HBV in West Africa for many years. They had also established the Gambia Hepatitis Intervention Study which aimed to evaluate both the short- and long-term outcomes of vaccination in West Africa. West Africa has one of the highest prevalence rates of HBV in the world and this is linked to a high incidence rate of hepatocellular carcinoma (HCC) which frequently presents in men between the ages of 30 and 50 years. Although the vaccine program promised to reduce the rate of HCC in the younger population there was no clinical or public health intervention to influence the rate of tumor incidence in those born before the vaccine was introduced.

We now have effective treatment, in the form of nucleoside and nucleotide analogs, which suppresses the virus and prevents progression to cirrhosis, development of decompensated cirrhosis and substantially reduces the risk of HCC. Like many others I felt that it was inappropriate to make the diagnosis of chronic HBV infection without being able to offer treatment.

Q Can you explain to our readers the significance of screening for HBV in the context of HCC, especially in Africa?

HBV infection is invariably asymptomatic meaning that individuals are rarely aware of their infected status. Treatment of HBV in patients before they develop cirrhosis prevents both cirrhosis and HCC and after patients have cirrhosis treatment prevents decompensation and reduces the risk of HCC by around 50% [5,6]. The majority of people who develop HCC in sub-Saharan Africa present with enormous tumors which are beyond any effective therapeutic intervention. Although poorly documented, the same is true for patients with decompensated cirrhosis in that they present at the very late stages of disease. In sub-Saharan Africa HCC is the leading cause of cancer mortality in males and the third most important in females [7]. The incidence rate of this tumor is almost exactly the same as the mortality rate due to lack of effective treatment and the late stage of presentation. HBV accounts for over 60% of HCC in Africa although this figure is probably an underestimate as some individuals will have lost hepatitis B surface antigen by the time they develop the tumor [8].

As HBV is the most important risk factor for HCC in West Africa many of us feel that

detection of HBV infection through screening would fulfill the criteria set out by Wilson and Jungner [9] for a screening program in that it is easily detected using tests for hepatitis B surface antigen, there are clear criteria for treatment as set out in European Association for Study of the Liver (EASL) guidelines, there is a long natural history between infection and end-stage disease, and there are treatments which are effective in changing the natural history. However, the missing component was the demonstration in a pilot study that screening was both effective and cost-effective. We therefore set up a pilot screening program in Gambia and in Senegal to show that community-based screening could be achieved and to evaluate the efficacy and cost-effectiveness of the procedure.

The vaccination programs for HBV began in most sub-Saharan countries in the late 1990s so that most children under the age of 18 are now protected against infection. This means that a screen and treat approach for HBV infection would only need to be conducted across a country on a single occasion unlike other screening initiatives. This should make the approach a highly cost-effective method of reducing the prevalence of HBV and the incidence of HCC.

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other screening initiatives. This should make the approach a highly cost-effective method of reducing the prevalence of HBV and the incidence of HCC.

As a member of the Executive Council of the PROLIFICA screening program, can you tell us a little about the program? What led to the development of the program? As part of the European Commission's Framework Programme 7 in 2010 a call was put out for research on virally induced cancers which involved countries from sub-Saharan Africa. This was an ideal opportunity to crystalize our plans for the development of screening and assessment program for HBV. The FP7 program also required us to explore and develop biomarkers for the prediction or diagnosis of HCC. We therefore involved partners from across Europe who had experience in metabolomics (Prof Simon Taylor-Robinson at Imperial College), proteomics (Dr Maimuna Mendy and Prof Chris Wild, International Association for Research on Cancer [IARC]), HBV virology (Dr Isabelle Chemin and Prof Fabien Zoulim, Inserm Lyon) and a small biotech company, Xeptagen (Venice) who have been developing tests for tumor antigens in serum.

Q What are the main objectives of PROLIFICA?

PROLIFICA has been set up with two platforms. The first is the West African Treatment Cohort for Hepatitis B (WATCH) which involves the community-based screening for HBV, the assessment of those who test positive for HBsAg and the treatment of those who meet international treatment guideline criteria. The second platform is the Hepatocellular Carcinoma Case-Control Cohort (HC4) which involves the collection of serum, plasma, DNA and urine samples from patients with HCC and controls who are either healthy community controls or HBV-infected controls without cancer. The main objectives for WATCH are to demonstrate the feasibility of community screening, evaluate rates of linkage into care and to enumerate the proportion of patients who require treatment. The data from this study will be used for health economic evaluation. We also propose to challenge the international guidelines by following the untreated HBV-infected patients to determine whether any of them develop end-stage liver disease. In

the treated patients, we hope to show that the rate of HCC development is reduced.

The main objectives for the HC4 study are to develop biomarkers which may be used either to predict the future risk of HCC or to help diagnose the tumor.

Q What changes do you hope to see with regard to diagnosis & treatment of HCC in resource-poor countries as a result of this program?

Primarily PROLIFICA is about prevention of HCC, however, we would like to think that the biomarker discovery program will generate novel diagnostics to help with HCC diagnosis. Alternatively, we may be able to stratify patients on the basis of biomarkers for high- or low-intensity surveillance based on risk of HCC development. Prof Taylor-Robinson's group have identified a pattern of urinary metabolites which distinguish patients with HCC from those who have cirrhosis or healthy controls [10,11]. These metabolites are detected using UPLC-MS methodology and were discovered in the metabolomics laboratories at Imperial. Waters Corporation have kindly donated one of their ultra high performance liquid chromatography - mass spectroscopy (UPLC-MS) machines which has been located in the MRC Laboratories in Gambia. This will now be used to measure the key urinary metabolites in real time to evaluate their diagnostic potential in clinical practice. If successful we acknowledge the need to transfer the measurement of these metabolites from the sophisticated MS device to a format which is more appropriate for resource-limited settings. We have even envisioned a urinary dipstick type system to provide the diagnosis.

In sub-Saharan Africa where the availability of triple-phase CT scanners is limited and liver biopsy is not feasible then a urine or serum-based assay which allows doctors or other healthcare professionals to distinguish HCC from other masses in the right upper quadrant would be invaluable. Although advanced HCC is not generally treatable competing diagnoses such as TB and lymphoma are amenable to therapy.

Clinical services in resource-limited settings are very variable but many countries are now able to offer liver resection and liver ablation for HCCs which are diagnosed at earlier stages of disease. It is hoped in the future that screening for HBV will be used to identify

high-risk individuals for ultrasound-based HCC surveillance. Once established, these sort of programs would be expected to pick up presymptomatic, early-stage tumors amenable to curative treatment.

Q In general, how do you see the diagnosis and management of HBV/HCC progressing over the next 5 years, both in the developing and the developed world?

I think there will be stark differences in the progression of diagnostics and therapeutics in the developed and developing world. In the developed world, we have moved away from invasive diagnostics over the last 10 years: HCC is one of the few major tumors where histology is not required for diagnosis. However, it is beginning to be clear that HCCs are very heterogeneous biologically and that it is naïve to expect all tumors to respond to chemotherapeutic agents in the same way. We will therefore be moving increasingly toward histological assessment with gene expression analysis to help stratify patients for treatment. In the developing world, as mentioned above the lack of acceptability/facility for biopsy and imaging may drive diagnosis to noninvasive tests. This is particularly relevant for patients who present at a late stage of disease when confirmation of the diagnosis is the only practical endpoint prior to initiating palliative care and in order to exclude treatable diagnoses.

What are the main obstacles that the medical community needs to overcome in this field? The prevention, diagnosis and treatment of HCC in resource-limited settings have a long list of obstacles to overcome. Primarily and perhaps most tangible to resolve is the training and provision of surgical and radiological expertise. Although I am optimistic about diagnostic

developments using noninvasive approaches there is also a desperate shortage of skilled histopathologists in resource-limited settings. The management of HBV infection is limited by the availability of molecular diagnostics to measure HBV DNA and where the assay is available the cost is prohibitive. For PROLIFICA, we have been able to set up our own laboratories running our own real-time PCR assays but this clearly cannot be extrapolated to all settings. There is an urgent need for a robust, reliable, accurate and cheap point-of-care assays for viral load monitoring.

However, the main obstacle to tackling HBV and HCC is the lack of political support. Despite 350 million people worldwide being chronically infected with HBV and a further 170 million infected with HCV, viral hepatitis is not listed as a major infectious disease by WHO. Furthermore, despite HCC being one of the top three causes of cancer mortality worldwide, there is remarkably little investment in research in this area.

Disclaimer

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