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EDITORIAL

European Association for the Study of the Liver and French hepatitis C recent guidelines: The paradigm shift

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Abstract

The latest Association Française pour l'Etude du Foie - French Association for Study of the Liver (AFEF) and European Association for the Study of the Liver (EASL) recommendations announce a change of paradigm, for the management of patients infected with hepatitis C virus (HCV). The AFEF recommendations focus on the elimination of HCV infection on a national level by preventing reinfection, in less than ten years. This goal involves the facilitation of patients' management in a simplified pathway by increasing screening procedures and access to pangenotypic treatments mainly in the "reservoir" population of people who inject drugs and migrants. Even in the complex pathway of patients with previous comorbidities, AFEF takes the option of a therapeutic simplification. The EASL guidelines position themselves on the state of the art with a precise description of all therapeutic options available, without separating simplified and complex pathways even if they take into account the epidemiological evolution of difficult-to-treat populations.

Key words: French; European; Hepatitis C; Guidelines; Pangenotypic; Direct acting antiviral drugs; Eradication; People who inject drugs; Migrants

Core tip: New French and European guidelines for the management of hepatitis C virus infection take into account the rapid change in the epidemiology of the infection and the arrival of short treatments, based on pangenotypic drugs with very few side effects. However, the French guidelines have a strong bias towards viral eradication with the elaboration of a simplified pathway for patients who are far from traditional healthcare structures.

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Hepatitis C treatment history extends over approximately a quarter of a century from standard interferon for non-A non-B hepatitis, through combination with ribavirin at the end of the 1990s, to the availability of pegylated interferon in the early 2000s. It took 25 years to go from 5% to 55% of sustained virological response (SVR). The arrival of new direct-acting antiviral agents (DAAs) has revolutionized hepatitis C management in the last five years, even if the first protease inhibitors (PIs) initially associated with pegylated interferon and ribavirin greatly increased the global side effects. In fact, very quickly after just over a year, next generation DAAs in interferon-free regimen were available.

As a first step, the cost of drugs which were recommended for severe patients in most countries limited their use: In 2014-2015, sofosbuvir-based regimens combined with simeprevir, daclatasvir or ledipasvir were reimbursed by the French health insurance only for severe fibrosis, extra-hepatic manifestations, human immunodeficiency virus (HIV)-co-infected, transplanted and hemodialysis patients, and this, despite a tremendous decrease of side effects and a shortening of treatments. The extension of indications to F2 fibrosis according to the METAVIR classification, corresponded in 2016 with the marketing of ombitasvir paritaprevir/ritonavir and dasabuvir and finally, in 2017, universal treatment access in France was official. In 2018, thanks to pangenotypic associations' availability, a really ambitious median term goal of virus eradication becomes increasingly realistic.

During a 5-year period, multiple American, European and national guidelines were proposed trying to follow the tremendous therapeutic revolutions. The last 2018 recommendations that correspond to the marketing of pangenotypic associations are a real paradigm shift. We will focus on French (AFEF, Association Française pour l' Etude du Foie - French Association for Study of the Liver) and European Association for Study of the Liver (EASL) recent guidelines, highlighting the marked strategic differences.

The EASL recommendations are the state of art on hepatitis C in 2018[1]. They aim at "describing the optimal management of patients with chronic HCV infection in 2018". The French recommendations are brief, simplified, and avant-garde[2]. Their goal is "the elimination of hepatitis C virus (HCV) infection in France" before 2025 if possible (Table 1).

Of course, both guidelines highlight the epidemiological changes. In France, for example, it is estimated that the majority of HCV patients are represented by people who inject drugs (PWID, 95000 estimated patients), 46% of them being viremic and to be treated. The second most difficult population to assess is the migrant population (90035 estimated patients), with 57% of them estimated to be viremic. Today, 90% of patients transfused before 1992 are diagnosed and treated[3,4].

Among PWID, 30% attend addiction centers and the others, who are difficult to quantify, consult general practitioners who deliver opioid substitution treatments (OSTs): In the French survey HEPCORT 2011, the prevalence of HCV seropositivity was 26% in general practice on patients under OSTs with so-called "non-problematic" consumption[5]. Another important source of contamination is prison in which 70% of prisoners are PWID for whom prevalence of anti-HCV antibodies is 4.8%, 46.4% being HCV RNA (+): Thus, 2.5% of detainees are viremic for HCV[6].

According to the French recommendations, elimination of HCV infection could be possible by 2025, 2030 according to the United States Global Burden of Disease. The different guidelines advocate the eradication of the virus, made possible thanks to simple diagnostic methods and highly effective treatments, provided that screening policies are intensified and access to treatment promoted. The first proposal of AFEF recommendations is to screen every adult at least once in his life for combined HBV and HIV and HCV viruses, and a 100% reimbursement of the screening tests. Moreover, the principle of "all inclusive" in the management of particular target populations requires the use of new screening methods. In addition to the rapid diagnostic tests (RDTs) which were known to have excellent sensitivity and specificity (99%)[7,8], but only detect antibodies, EASL mentions the need for the development of Core Ag, dried blood spots, allowing HCV RNA rapid availability in patients who are difficult to collect. The principle of "reflex testing" is still in the experimental stage but is a way to obtain real time HCV RNA even if many problems remain to be solved including the cost.

The need for pre-therapeutic genotyping is addressed by AFEF and EASL. In the area of the availability of pangenotypic therapeutic associations, both guidelines consider that genotyping is not mandatory: In a "simplified pathway" for AFEF, or "in areas where genotyping is not available and/or not affordable, or simplify treatment access" for EASL. However, screening for initial fibrosis remains the key for both academic societies in simplified pathways for specific populations and in complex or specialized pathways. It determines the duration of the treatment and is essential for the follow-up especially the long-term detection of complications such as hepatocellular carcinoma or portal hypertension. FibroScan® (transient elastography) that measures liver stiffness in a non-invasive way is an educational and motivational tool for AFEF, qualities that were confirmed in several experiments available in addiction centers[9-11].

AFEF proposes FibroScan® or complex fibrosis biological tests thresholds, to rule out the diagnosis of severe fibrosis and therefore to identify patients who will not require prolonged follow-up after virological cure except for the presence of hepatic co-morbidities (Liver stiffness with FibroScan® < 10 kPa or FibroTest® ⩽ 0.58

Table 1 French and European Association for the Study of the Liver recommendations principal similitudes and differences

	French recommendations	EASL recommendations
Target audience	National	European, international
Philosophy	Goal of HCV eradication Maximum simplification of HCV management	State of art
Screening	Global "Test and treat"	Global "Test and treat"
Fibrosis	FibroScan®, FibroTest®, FibroMeter®	Enlarged to simple and accessible biological methods, APRI, Fib4
RAS screening	Only in case of previous failure to DAA treatment	May be used, in addition and if available, before treatment to optimize some non pangenotypic strategies
Prescribers	Hepatologists or general practitioners	Hepatologists
Regimens	Preferably pangenotypic associations sofosbuvir - velpatasvir 12 wk or glecaprevir - pibrentasvir 8 wk if no severe fibrosis	Pangenotypic and no pangenotypic associations according to genotype, viral load, degree of fibrosis, previous treatment, and eventual RAS No sofosbuvir - velpatasvir in case of G3 cirrhotic patients
In case of failure	RAS screening Only for first generation DAAs failures Sofosbuvir - velpatasvir - voxilaprevir 12 wk, sofosbuvir - velpatasvir - voxilaprevir with or without ribavirin 12-24 wk in G3 cirrhotic patients	RAS screening In addition, for patients with poorer prediction of response sofosbuvir - glecaprevir - pibrentasvir and sofosbuvir - velpatasvir - voxilaprevir 12-24 wk with or without ribavirin according to multidisciplinary decision
Decompensated cirrhosis	Regimen without protease inhibitors	Regimen without protease inhibitors
Renal insufficiency	Glecaprevir - pibrentasvir or, grazoprevir - elbasvir (G1) 12 wk	Glecaprevir - pibrentasvir or grazoprevir - elbasvir (G1), 8-12 wk

APRI: Aspartate aminotransférase to Platelet Ratio Index; DAA: Direct acting antiviral; EASL: European Association for the Study of the Liver; HCV: Hepatitis C virus; RAS: Resistance-associated substitutions.

or FibroMeter® $\leqslant$ 0.786). EASL retains APRI and FIB4 as an alternative in the absence of other local resources, even if the sensitivity and specificity are worse[12]. If FibroScan®, FibroMeter® and FibroTest® are easily available in France and many European countries, APRI and FIB4 can be instantly applied in all geographical area. For both academic societies, the screening strategy of particular populations in a "test and treat" goal, is therefore crucial and demonstrates an individual but also collective benefit.

The collective benefit, treating to prevent contamination in PWID has been demonstrated in various English, Australian and Icelandic experiments[13,14]. Interestingly, in several Eastern European countries, it has been shown that a global strategy - increasing screening, risk prevention with access to sterile syringes, in situ delivery of antiviral treatment associated with OSTs - reduced by almost 80% new HCV cases while the prescription of DAAs alone had an impact of only 10%[15]. Finally, one study unexpectedly suggested that accepting a diagnostic test for HCV in substitution centers, whether positive or negative, could have an impact on drug use[16].

Apart from these findings, the French recommendations commit themselves to a more proactive approach to facilitate diagnosis, treatment and eradication: "The treatment of hepatitis C must be prescribed by all doctors", "Treatment monitoring can be performed by non-medical caregivers", "Direct antiviral agents should be available in all pharmacies". Prescription by all doctors might be still a little premature and requires a culture change and systematic training. In a recent Australian experiment[17], dating from 2016, the opening of the prescription to general practitioners allowed access to treatment of rather disadvantaged populations, far from urban areas; however, much remains to be done as 58% of these prescriptions represented less than 12% of hepatitis C cases. Cost reduction and second-generation treatments generating fewer drug interactions, have allowed direct prescribing of DAAs without prior multidisciplinary consultation except in the following difficult cases: Prior DAA treatment failure, chronic renal disease, severe cirrhosis, liver cancer, co-infection with HBV or HIV, transplantation. Task delegation for therapeutic follow-up is possible as it was suggested that patients' attendance at consultations in addiction treatment centers was better with nurses than with general practitioners and specialists[18] and comparable results were experienced with the inmates[19].

Of course, according to AFEF recommendations, certain conditions are unavoidable for universal prescribing in a simplified pathway by non-specialists: Absence of HBV and/or HIV co-infection, severe renal insufficiency (eGFR < 30 mL/min per 1.73 m²), poorly controlled hepatic comorbidities (risky alcohol consumption, diabetes and obesity), severe hepatic disease, prior DAAs therapy. After ruling out the diagnosis of severe fibrosis by non-invasive methods, and in the absence of genotyping determination in the simplified pathway, the two pangenotypic therapeutic options recommended are: Sofosbuvir + velpatasvir for 12 wk and glecaprevir + pibrentasvir for 8 wk. A simple evaluation of the drug interactions is easy to do by consulting the website: https://www.hep-druginteractions.org/ or by using the smartphone app HEP iChart. Virological cure must be assessed by measuring viral load 12 wk after stopping treatment. All patients who do not meet these specifications are taken care of in a specialized pathway.

EASL guidelines do not distinguish between two types of patient pathways, even though specificities related to the management of PWID are clearly reported: Screening methods described above, *in situ* HCV RNA evaluation or easier, core antigen undetectability in serum or plasma 24 wk (SVR24) after the end of treatment, are an alternative endpoint of therapy in patients with detectable HCV core antigen prior to therapy.

In specialized patient pathways, AFEF recommendations also have a simplification bias focusing on the recommendations of pangenotypic associations. A minimal opening for non-pangenotypic options is left with the pre-requisite, of course, of systematic genotype knowledge: Sofosbuvir ledipasvir for G1 without severe fibrosis and grazoprevir elbasvir for genotype 1b, genotype 1a with an initial viral load ⩽ 800000 IU/mL and treatment naive genotype 4.

Some differences between both academic societies can be highlighted: EASL states the possibility of an 8-wk treatment with grazoprevir elbasvir for patients with genotype 1b[20] without severe fibrosis, and still finds relevant the ombitasvir paritaprevir dasabuvir combination for genotypes 1b or 4, during 8 or 12 wk whereas AFEF considers this combination obsolete. In many geographic areas however, this latter combination stays as a very good option, as studies from real life demonstrate its efficacy and safety in chronic hepatitis C, even in people with compensated liver cirrhosis[21].

A divergent point is also, according to EASL, the absence of recommendation of sofobusvir velpatasvir for G3 cirrhotic patients, the expected response being suboptimal (89% to 93% SVR)[22], while the AFEF maintains the indication of the association in this circumstance in a simplification goal.

The determination of pre-therapeutic resistance-associated substitutions (RAS) in situations that could have been demonstrated useful for some initial therapeutic options is no longer relevant for AFEF. On the other hand, EASL specifies that "in areas where only regimens that require optimization based on pre-treatment resistance testing are available, and physicians have easy access to a reliable test that evaluates HCV resistance to NS5A inhibitors", these analyses can guide decisions, as specified in the EASL recommendations for treatment of hepatitis C 2016[23].

In decompensated cirrhosis, conventionally managed by pangenotypic combinations without PIs and with ribavirin at standard doses, EASL states that increasing doses of ribavirin may be tested in terms of tolerance, and that a 24-wk regimen without ribavirin is possible in patients who have a contraindication or are intolerant to ribavirin.

AFEF only gives recommendations for patients who failed first-generation DAAs: Sofosbuvir + velpatasvir + voxilaprevir for 12 wk[24]. In genotype 3 patients without cirrhosis, the SVR was higher than in patients with cirrhosis, respectively 99% *vs* 93% and, sofosbuvir + velpatasvir + voxilaprevir with or without ribavirin for 12 to 24 wk was recommended for genotype 3 patients with cirrhosis (expert opinion). However, EASL offers solutions for patients with poorer prediction of response (several lines of treatment, advanced disease, complex RAS anti NS5a) in a multi-disciplinary decision: Sofosbuvir + glecaprevir + pibrentasvir for 12 wk[25,26] and for very difficult to retreat DAAs failures (NS5A RASs after at least two failures of a PI and an anti-NS5a): Sofosbuvir, velpatasvir, voxilaprevir + ribavirin or sofosbuvir + glecaprevir + pibrentasvir + ribavirin, and in case of intolerance to ribavirin an extension of treatment, from 16 to 24 wk (expert opinion).

For both academic societies, the post-transplantation treatment must be initiated early on stabilization (3 mo) of the patient and must include immunosuppression with therapeutic drug monitoring (TDM) of immunosuppressive (IS) treatments during DAAs treatment and after cessation. AFEF proposed sofosbuvir + velpatasvir for 12 wk or glecaprevir + pibrentasvir for 12 wk. EASL recommends mainly sofosbuvir + velpatasvir or sofosbuvir + ledipasvir without IS dose adjustments and glecaprevir + pibrentasvir only if eGFR < 30 mL/min per 1.73 m² and with IS dose adjustments. In fact, IS dose adjustment is essential regardless of the therapeutic associations used, even if the risk of imbalance of immunosuppression is greater with glecaprevir and pibrentasvir.

In case of renal insufficiency, for AFEF and EASL, if the eGFR is < 30 mL/min per 1.73 m^2, the available treatments are glecaprevir + pibrentasvir or, for genotype 1 infections grazoprevir + elbasvir. The AFEF advocates uniform treatment duration of 12 wk and EASL applies the classic rules of 8 to 12 wk even if the available clinical trials were carried out over 12 wk.

Finally, in this time of scarcity of grafts, organ transplantation from a HCV + RNA + patient to another HCV + RNA + patient is allowed. EASL offers the same option for HCV-RNA-patients provided that the patient's informed consent is obtained and that post-transplant antiviral therapy is available and very quickly proposed. In France, this possibility is not yet recognized by the official agencies but this should be the case in the near future.

In conclusion, the latest AFEF and EASL recommendations announce a change of paradigm, for the management of hepatitis C. The EASL recommendations are very detailed and describe almost all the therapeutic options. The AFEF recommendations focus on the simplification of HCV management with an eradication objective to prevent reinfection thus better taking into account the epidemiological evolution and the change of culture with respect to the disease, according to us. Patients including mainly PWID and migrants should be treated massively in a simplified way facilitated by the availability of very effective and devoid of side effects pangenotypic drugs. The philosophy of the "all inclusive" or the "talk, test and treat" will involve other actors than hepatologists in a global vision of health care of these

particular populations with a culture of task delegation.

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