Ledipasvir + sofosbuvir

ATC codes: J05AP51

Indication	Chronic hepatitis C ICD11 code: 1E51.1
INN	Ledipasvir + sofosbuvir
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 90 mg + 400 mg tablet
EML status history	First added in 2015 (TRS 994)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	Ledipasvir + sofosbuvir
DrugBank	Ledipasvir, Sofosbuvir

Expert Committee recommendation

The Expert Committee recommended the inclusion of all of the requested direct-acting antivirals on the core list of the EML, under a new section (Medicines for the treatment of Hepatitis C) and subsections (pharmacological classes). The Committee intends to review these recommendations regularly in line with evolving WHO guidelines. Currently available direct-acting all-oral antiviral regimens (with or without ribavirin) for treatment of chronic HCV infection show significantly improved SVR12 rates and reduced side-effect profiles compared with interferon-based regimens. However, optimal use of these medicines requires multidisciplinary, specialist medical care as well as diagnostic tests for HCV (i.e., genotyping and viral load measurement); these are currently expensive and have limited availability in many countries, which may limit uptake and access, even where the drugs are affordable. Thus, the ideal scenario is a simple diagnostic assay to establish HCV infection (e.g. buccal swab), a highly effective, affordable and well-tolerated once daily pan-genotypic medication to be taken for a limited period (8–12 weeks or less) and a single blood test 12 weeks after therapy is completed to establish the clearance of chronic hepatitis C infection. Noting and accepting the clinical benefit of the new DAAs, the Expert Committee recommended that an interferon-free DAA combination regimen should be the preferred option for treatment of hepatitis C, as it avoids the substantial toxicity associated with interferon use. However, DAA monotherapy should not be used because of its poor efficacy and the potential for development of resistance. The Committee recognized that interferon-containing regimens have a place in the treatment of some patients. As the treatment regimens are still being developed and are changing rapidly, the Expert Committee recommended that the List present the products subdivided by pharmacological class, as for the presentation of anti-HIV medicines. The expectation is that, in the future, there will be options within classes so that a square box listing may be

appropriate. Inclusion on the EML of all DAAs proposed in the applications received aims at promoting competition among available alternatives and allowing for the selection of optimal combination treatment regimens, which may or may not be existing fixed-dose combinations. The Committee also recommended that WHO continue to work on existing approaches to managing prices and evaluate alternative strategies to improve affordability and access in order to reduce the global burden of chronic HCV infection.

Background

Five applications for direct-acting antiviral (DAA) regimens were considered by the Expert Committee for addition to the Model List for the treatment of chronic hepatitis C virus (HCV) infection: sofosbuvir, daclatasvir, simeprevir, ledipasvir + sofosbuvir (fixed-dose combination (FDC)), and ombitasvir + paritaprevir + ritonavir (FDC), with or without dasabuvir. Daclatasvir had not previously been considered by the Expert committee for inclusion on the EML. An overview of HCV medicines that are currently available, or that are in advanced clinical development, was received from the Treatment Action Group (TAG) (1). The Expert Committee discussed the available and forthcoming DAA regimens and considered the research gaps in the treatment for HCV on the basis of the TAG report. The Expert Committee acknowledged the importance of approved new DAAs for hepatitis C, the promising pipeline of drugs in development, and determination of optimal DAA regimens with best-in-class drugs as an area in need of a public health research agenda.

Public health relevance

The global burden of chronic hepatitis C is enormous with an estimated 185 million infected worldwide and 350,000 HCV-related deaths per year (2). The worldwide prevalence of hepatitis C infection varies substantially. Egypt has the highest prevalence with more than 15% of the population infected and Africa has an estimated HCV seroprevalence of 3%. Further, due to shared routes of transmission, co-infection with HIV and HCV is common, with approximately 4–5 million persons co-infected with HCV/HIV worldwide (3). Data from a large cohort of patients with HCV (more than 120 000) from the US Veterans Administration showed that only 24% of patients received treatment following HCV diagnosis and that only 16% of treated patients achieved an undetectable viral load (HCV RNA) after treatment (4). The observed low percentage of patients receiving treatment would suggest that up until now, most patients were “either healthy or too sick for hepatitis C treatment” (5). A 2013 study evaluating treatment uptake in 16 countries reported that, in nine of the countries, less than 1.5% of the HCV-infected population received treatment and that the treatment rate exceeded 5% only in France. The authors concluded that the current rates of treatment and efficacy are inadequate to address the burden of disease associated with HCV (6). HCV is classified into 6 genotypes (and subtypes) with distinct geographical distribution. In general, genotype 1 is the most common, accounting for approximately 46% of infections, and genotype 3 has a global prevalence of approximately 30%. Due to variable genotype-dependent treatment responses, current regimens require HCV genotype testing. Identification of host single nucleotide polymorphism of the interleukin 28B (IL28B) gene on chromosome 19, which varies markedly by ethnic group, may be useful in predicting response to HCV therapy (7). Assessment of HCV viral load (i.e. HCV RNA) is required both before and after HCV treatment. These tests are frequently unavailable in resource-poor countries. The standard antiviral treatment regimen for all HCV genotypes was based for many years on pegylated interferon (PEG-IFN) injections and oral ribavirin (RBV) (8). PEG-IFN/RBV treatment was limited by partial response, with achievement of a sustained virological response (SVR, defined as undetectable serum HCV RNA by a clinical polymerase chain reaction assay at 12–24 weeks following the end of treatment) in less than 50% of patients (1). Treatment regimens with PEG-IFN/RBV were complex and resource-intensive and were accompanied by significant adverse events; the suboptimal treatment responses resulted in large numbers of patients ultimately progressing to cirrhosis. In contrast, patients who achieve an SVR experience a reduction in liver inflammation and in the rate of progression of liver fibrosis. Several long-term observational studies have shown that achievement of an SVR has been associated with fibrosis regression and reduced risk of hepatocellular carcinoma. Reductions in all-cause mortality have also been observed (8, 9), highlighting the benefits of treating patients with advanced liver disease. However, PEG-IFN requires subcutaneous administration, must be used with caution in cirrhotic patients because of the risk of precipitating liver decompensation, and is not recommended in patients with decompensated

cirrhosis as it can cause significant morbidity and mortality (10). Additionally, RBV requires twice-daily dosing, is associated with haemolytic anaemia and is highly teratogenic. Thus RBV-sparing regimens are also highly desirable. The advent of effective, well-tolerated, IFN-free treatments means improved treatment options for patients with advanced liver disease. Patients with significant fibrosis should thus be prioritized for treatment. However, patients with chronic hepatitis C at an earlier stage can also benefit, with progression to late stage of disease being interrupted and the risk of other extrahepatic complications of infection reduced. Expanding anti-HCV treatment capacity to target patients at risk of infecting others is also beneficial from a public health perspective. Several new anti-HCV DAA regimens proposed for inclusion on the EML have been developed and registered in recent years. These new treatments have been shown to be more effective, better tolerated and safer than the older therapies (i.e. PEG-IFN/RBV in combination with first-generation protease inhibitors or DAAs such as boceprevir and telaprevir); several also exhibit broader genotypic activity than previous options. It is expected that inclusion of the proposed DAAs in the Model List will help facilitate the global scale-up of chronic hepatitis C treatment and focus the attention of all stakeholders on the need to increase the affordability of and access to DAAs.

Benefits

Ledipasvir (90 mg) and sofosbuvir (400 mg) have been co-formulated as an oral once-daily fixed-dose combination indicated for the treatment of HCV genotype 1 infection in adults. The FDC is highly effective for both treatment-naïve and experienced patients, even those with cirrhosis. The duration of therapy with ledipasvir + sofosbuvir is 12 weeks for treatment-naive and noncirrhotic treatment-experienced patients and 24 weeks for cirrhotic treatment-experienced patients. Eight weeks of treatment may be sufficient in treatment-naïve non-cirrhotic patients with a viral load less than 6 million IU/mL at baseline. In most patient populations, efficacy does not appear to be significantly improved by the addition of RBV. However, in treatment-experienced cirrhotic patients with HCV genotype 1 infection who failed sequential treatment with PEG-IFN/RBV as well as PEG-IFN/RBV protease inhibitor-based therapy, the combination of sofosbuvir + ledipasvir + RBV for 12 weeks or sofosbuvir + ledipasvir for 24 weeks resulted in SVR12s of 96% and 97% respectively (11). The efficacy of ledipasvir + sofosbuvir FDC was evaluated in several phase III studies in patients with HCV genotype 1 infection (11-16). The trials showed very high SVR rates at 12 weeks (> 90%) in both treatment-naive patients and treatment-experienced patients (14, 16) SVR rates were also consistently high (> 90%) among different subgroups, including those that usually have been considered poor responders to interferon-based treatment (e.g. non-CC IL28B genotype, high viral load at baseline, black race, genotype 1a infection). A shorter duration of therapy also appears to be highly effective in patients without cirrhosis (14). Extension of the treatment to 24 weeks and addition of ribavirin did not substantially increase SVR (12, 14, 17), except in the subgroup of treatment-experienced cirrhotic patients who failed prior triple therapy with a protease inhibitor/PEG-IFN and RBV, as noted above (11). Available data on the efficacy of ledipasvir + sofosbuvir FDC in patients with non-genotype 1 HCV are limited. The application stated that data (on file) from small patient populations in phase II trials suggest treatment is associated with high cure rates in patients with genotypes 3, 4 and 6 HCV infection. HCV resistance monitoring showed that sofosbuvir has a high genetic barrier to resistance, and that efficacy of the FDC remained high despite the presence of specific baseline mutations (12, 14, 16).

Harms

A good safety and tolerability profile with a very low rate of discontinuations has been demonstrated for ledipasvir + sofosbuvir FDC. The most common adverse events were fatigue, headache and insomnia (16). Serious adverse events were reported by a minority (< 8%) of patients, and most adverse events were considered to be unrelated to treatment.

Cost / cost effectiveness

In the USA, the entry prices for sofosbuvir (used in combination with ribavirin) and ledipasvir/sofosbuvir were US$ 84 000 and US$ 94 500, respectively, for a 12-week course, and the launch price for a 12-week treatment course with co-formulated ombitasvir + paritaprevir + ritonavir with or without dasabuvir was US$ 83 300. The

approximate price of generic ribavirin is US$ 700 for 12 weeks. Although these prices are extremely high, substantial price reductions have been achieved through special agreements on tiered prices with the originator companies. For example, Egypt negotiated a 99% price reduction for sofosbuvir to US$ 900 for a 12-week course. Jurisdictions in some high-income countries have also negotiated significant discounts on listed prices with different manufacturers, and WHO is working to promote the rapid introduction of prequalified generic formulations as well as supporting countries/jurisdictions in negotiating lower drug prices. Nevertheless, widespread access to interferon-free combinations is limited by high total costs in most healthcare systems. Evidence from two recent studies suggests that the manufacturing costs for a 12-week all-oral DAA regimen could be a fraction of current market prices (18, 19). Specifically, the analyses suggest that 12-week regimens could cost as little as US$ 118 for the as-yet unapproved Merck DAA combination, US$ 149 for treatment with sofosbuvir plus ribavirin and US$ 193 for sofosbuvir + ledipasvir. This cost analysis has not been completed for the ombitasvir + paritaprevir + ritonavir and dasabuvir combination, but it is reasonable to suppose that similar manufacturing costs might result. The Expert Committee saw reason to believe that significant price reductions could be achieved. In the application for sofosbuvir, the manufacturer (Gilead) states “three basic pricing bands have been set to serve as the starting point for negotiations with national governments. Countries are categorized within the bands according to gross national income per capita and hepatitis C prevalence. Final prices are determined on a country-by-country needs basis.” Gilead issued voluntary licences to seven Indian generic companies to produce sofosbuvir and market it in 91 countries (excluding Brazil and China) (20). Less is known about the plans of other companies (notably AbbVie, Janssen and BMS) to ensure widespread access to their medicines in low- and middle-income countries (LMICs). Affordability and opportunity cost in the context of a country’s total health or pharmaceutical expenditure need to be considered before widespread access to treatment can become a reality: it is only with low prices that widespread access to HCV treatment in LMICs could become a realistic goal. Inclusion in EML should also provide the impetus for countries to use pricing policies known to be effective in reducing prices and promoting competition, through means such as voluntary or compulsory licences, procurement strategies (e.g. tendering, pooled procurement), and generic substitution (when quality-assured generic products are available).

WHO guidelines

In April 2014, WHO issued guidelines for treating hepatitis C (2), which will be updated on a regular basis as new drugs and new research findings become available. The 2014 guidelines strongly recommend sofosbuvir- and simeprevir-containing regimens. The Expert Committee acknowledged that, based on multiple clinical studies, use of DAA-containing regimens results in much higher SVR rates assessed at 12 weeks post-treatment (i.e. SVR12) than IFN-based regimens. The new regimens generally have response rates in excess of 90% in both treatment-naive and previously treated patients and an improved adverse event profile; treatment duration is reduced and administration and monitoring are simplified.

Other considerations

In general, the Expert Committee considered that DAAs (individually and used within the considered regimens) are effective and well tolerated. However, the Committee noted that there is as yet no substantial experience with the safety and effectiveness of these medicines in real-life, non-trial settings, particularly in patients living in low- and middle-income countries. In the USA, the “real-world” TARGET study showed overall approximately 10% lower rates of SVR compared with clinical trial data (21). In addition, several new hepatitis C drugs are in advanced clinical development or submitted for regulatory approval. Merck have developed a novel regimen consisting of grazoprevir (an NS3/4A protease inhibitor) and elbasvir (an NS5A inhibitor), which demonstrated high SVR12 rates in treatment-naive cirrhotic and non-cirrhotic patients with genotype 1, 4 or 6 infections. Virological failure was associated with baseline NS5A polymorphisms and emergent NS3- or NS5A-resistant associated variants (RAVs) or both (22). The magnitude of the effect and the consistency of safety and efficacy data across various patient groups and genotypes highlight the importance of DAAs as key, essential medicines to treat HCV. With expanded use in populations that have been excluded from trials, new adverse events and drug–drug interactions may be expected to emerge and should be monitored. Moreover, as with HIV, the evolution and emergence of drug

resistance (i.e. RAVs) should be monitored globally (23). Given the challenges of using existing diagnostic tests, highly effective, pan-genotypic treatment strategies that do not require these tests should become the focus of a global approach and a priority for independent research, with clinical trials comparing various DAA combinations. The Expert Committee also noted the need for robust clinical trials to assess the suitability of DAAs for use in paediatric patients and for determination of appropriate, therapeutic anti-HCV regimens in the paediatric population.

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