Attitude and Practices Regarding Use of Direct Acting Antiviral Agents (DAAs) in the Treatment of Hepatitis C among Health Care Practitioners “A Survey-based Study”

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Authors’ contributions

This work was carried out in collaboration among all the authors. Author NS designed the study, wrote the protocol along with the first draft of the manuscript. Author AW performed the statistical analysis. Authors DZ and SS managed the literature searches and final drafting. Authors UZ and AA did all the final setting and helped in manuscript writing. All the authors read and approved the final manuscript.

ABSTRACT

Approximately 3% of the world population has been known to be infected with HCV. Hepatitis C virus is a major etiological factor behind the development of liver diseases such as cirrhosis and hepatocellular carcinoma. Interferon-based therapy has remained as the mainstay treatment for HCV for decades. Owing to the unavoidable side effects of interferon, direct-acting antivirals (DAAs) have been approved recently for the treatment of HCV-infected patient. These drugs have brought revolution in the management of HCV because of their favorable side effects profiles and enhanced rates of sustained virological response. We conducted a questionnaire-based survey study to assess the knowledge and current practices among specialists and senior post graduate trainees regarding treatment of HCV with DAAs. The questionnaire was based on latest WHO
1. INTRODUCTION

Hepatitis C virus (HCV) blood-borne pathogen which is of significant concern globally. (Stanaway et al, 2016). After the infection with the virus, there is acute infection which can progress to chronic infection in 80% of the cases [1] and therefore resulting in severe complications such as liver cirrhosis [2] and hepatocellular carcinoma [3]. HCV is a blood-borne virus which may transfer through injection drug use, unsafe injection practices, unsafe health care, transfusion of unscreened blood and blood products, and sexual practices that lead to exposure to blood [4]. HCV can cause both acute and chronic hepatitis, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. The incubation period for hepatitis C ranges from 2 weeks to 6 months. Following initial infection, approximately 80% of people do not exhibit any symptoms. Those who are acutely symptomatic may exhibit fever, fatigue, decreased appetite, nausea, vomiting, abdominal pain, dark urine, grey-coloured faeces, joint pain and jaundice [5]. HCV acts as an enormous economic burden on health care systems due to morbidity and mortality associated with it as around 71 million people are affected worldwide [6]. WHO has set goals for the elimination of HCV infection by 2030 [7]. Direct-acting antivirals (DAAs), which are considered highly effective in the treatment of chronic HCV are expected to reduce HCV disease burden [8]. The most affected areas of the world are Middle East and North Africa with 15 million people suffering from chronic infection [6]. As far as Pakistan is concerned it is mainly endemic with prevalence of 4.8% according to the national survey done in 2007-2008 [9]. The transmission of the infection is widespread reported by both healthcare and community settings [10]. There is an immense need for targeted and cost-effective prevention and treatment regimens against HCV to meet the global target of HCV elimination [11]. Interferons were the initial line of treatment for the patients of hepatitis C with ribavirin (RBV) for achieving cure rates [12] but the interferon therapy is now being discouraged due to its side effects such as flu-like symptoms, hematological toxicity, elevated transaminases, nausea, fatigue, and psychiatric sequelae [13,14]. Recently direct acting antiviral agents (DAAs) that targets various stages of HCV lifecycle have been developed [15]. The advent of direct-acting antivirals (DAAs) initiated the era of high efficacy and well-tolerated medications with high cure rates [11]. Around the globe many professional societies have updated their treatment guidelines to include DAAs as first-line treatment [16]. The dawn of these new treatments has played a significant role in WHO updating its treatment protocols for the elimination of this deadly viral hepatitis [17]. This research attempts to understand the existing protocols of Hepatitis C treatment and how it is followed in our public sector, by understanding the current practice of health care practitioners regarding the use of new regime of DDAs according to latest WHO guidelines. These guidelines aim to provide evidence-based recommendations on the care and treatment of persons diagnosed with chronic HCV infection.

2. METHODOLOGY

2.1 Study Design

The study was a cross-sectional survey, using convenient sampling.

2.2 Study Area

The study was conducted at Civil Hospital Quetta, a public sector tertiary care setup.

Keywords: Awareness; current practices; hepatitis C treatment; direct-acting antiviral agents.
2.3 Population of Interest
Total 112 health practitioners were surveyed in this study. The survey form was specifically designed to obtain information from a specific type of study population which includes consultants and senior Post Graduates posted in Gastroenterology and Internal medicine departments. All the participants in study contributed voluntarily.

2.4 Sampling
After the written informed consent, they were given a pretested and pre-validated likert-scale type questionnaire ranging from 1 to 5, 1- Strongly disagree, 2- Disagree 3- Neutral 4- Agree 5-Strongly agree contributing close ended questions plus two open ended questions related to practice and awareness regarding use of DAAs according to the latest updated guidelines issued by WHO for the treatment of hep C. The demographic information of participants was limited to age, gender and educational level.

2.5 Research Objective
To assess the knowledge, awareness and practices regarding among specialists and senior post graduate trainees while treating hepatitis C patients with DAAs.

2.6 Statistical Analysis
The data was entered and analyzed by using SPSS version 20. The descriptive analysis was used to report the demographics, field of practice and location of primary practice. Frequency and percentage were reported for qualitative variables. The knowledge about diagnosis, treatment and practices were displayed in tabular form. Assessment of knowledge about diagnosis, treatment and practice were based on statements, and these statements were based on 5-point Likert scale ranging from strongly agree to strongly disagree.

3. RESULTS

3.1 Demographics of the Practitioners
A total of 112 physicians were surveyed. The overall response rate was 50%. Practitioner and practice characteristics are summarized in Table 1. Majority (95%) of practitioners were between the age of 21-30 years and mostly (69.6%) were females. Enrolled physician’s level of education was predominantly post graduate trainee (86.6%) and mostly (94.6%) showed medical officer as academic rank. Furthermore, most of them were from Internal medicine department (88.4%) and work in public sector (97.3%).

3.2 Conventional Treatment of Hepatitis C
Practitioners reported varying opinion on conventional treatment with interferon in combination with ribavirin as mentioned in Table 2. Almost 60% practitioners observed recurrence with interferon therapy and 70% responded that patients quit interferon treatment due to unbearable side effects. Most of the physicians (56%) mentioned that patients do not show high rates of sustained virological response (SVR) after completing interferon therapy. Two third physicians disagreed regarding funds allocation by government for HCV treatment.

3.3 Direct Antiviral Agents (DAAs)
Almost three-fourths of the practitioners are aware of direct antiviral agents (DAAs) and 70.2% agree that DAAs reduce the duration of treatment along with low bill burden and less side effects. Majority (56%) of the physicians disagreed to treat pregnant and lactating patients with DAAs. Most of the physicians (47.3%) showed neutral response towards prescription of DAAs for children below 12 years of age.

3.4 Preference of DAA over Interferon Therapy
Four out of five physicians responded that they prefer direct antiviral agents (DAAs) over conventional treatment interferon. However, 79.4% of physician agree to prefer direct antiviral agents (DAAs) over interferon therapy in practice. Moreover, 71.4% of physician agreed that treatment with DAAs give more successful rate of sustained virological response (SVR) while 28.6% physicians had neutral response, however none of them disagreed with it.

3.5 Genotypic Regimens
Most of the physicians (71.4%) go for genotyping before starting treatment with DAAs and three-fourth practitioners agree that genotype 3a is the most prevalent type of HCV in Pakistan. Moreover, 65.2% of participants think that pan genotypic regimens eliminate the need for genotyping. However, practitioners were not very much satisfied with the availability of pan genotypic combinations of DAAs to the patients.
### Table 1. Demographic data of the participants

| Indicators          | Frequency | Percentage (%) |
|---------------------|-----------|----------------|
| **Age**             |           |                |
| 21-30               | 95        | 84.8%          |
| 31-40               | 10        | 8.9%           |
| 41-50               | 5         | 4.5%           |
| 50 above            | 2         | 1.8%           |
| **Gender**          |           |                |
| Male                | 34        | 30.4%          |
| Female              | 78        | 69.6%          |
| **Level of education** |        |                |
| PG trainee          | 98        | 87.5%          |
| MCPS                | 2         | 1.8%           |
| FCPS                | 12        | 10.7%          |
| **Academic rank**   |           |                |
| Medical officer     | 106       | 94.6%          |
| Senior Registrar & Above | 6    | 5.4%           |
| **Field of practice** |       |                |
| Gastroenterology    | 9         | 8.0%           |
| Hepatology          | 2         | 1.8%           |
| Internal medicine   | 99        | 88.4%          |
| Primary care        | 2         | 1.8%           |
| **Location of primary practice** | |                |
| Public sector       | 109       | 97.3%          |
| Private sector      | 1         | 0.9%           |
| Both                | 2         | 1.8%           |
| **Total Number of Participants** | 112 | 100.0%        |

### Table 2. Knowledge about genotyping and treatment of HCV

| Knowledge about genotyping and treatment of HCV | Strongly disagree | Disagree | Neutral | Agree | Strongly agree |
|------------------------------------------------|-------------------|---------|---------|-------|---------------|
| Do you think that hep C should be treated with medication such as interferon in combination with ribavirin? | 4                 | 33      | 35      | 28    | 12            |
|                                                 | 3.6%              | 29.5%   | 31.3%   | 25.0% | 10.7%         |
| Have you seen patients who are treated with interferon therapy coming with recurrence of disease? | 1                 | 15      | 30      | 52    | 14            |
|                                                 | .9%               | 13.4%   | 26.8%   | 46.4% | 12.5%         |
| Do patients quit interferon treatment due to unbearable side effects? | 3                 | 6       | 25      | 60    | 18            |
|                                                 | 2.7%              | 5.4%    | 22.3%   | 53.6% | 16.1%         |
| Do patients show high rates of sustained virological response (SVR) after completing interferon therapy? | 0                 | 27      | 36      | 43    | 6             |
|                                                 | 0.0%              | 24.1%   | 32.1%   | 38.4% | 5.4%          |
| Are there enough funds allocated by government for HCV treatment? | 23                | 51      | 20      | 13    | 5             |
|                                                 | 20.5%             | 45.5%   | 17.9%   | 11.6% | 4.5%          |
| Are you aware of Direct antiviral agents (DAAs)? | 2                 | 13      | 15      | 65    | 17            |
|                                                 | 1.8%              | 11.6%   | 13.4%   | 58.0% | 15.2%         |
| Do you treat patients exclusively with DAAs? | 3                 | 17      | 13      | 60    | 19            |
|                                                 | 2.7%              | 15.2%   | 11.6%   | 53.6% | 17.0%         |
| Do you think that DAAs have short duration, low pill burden, bearable side effects profile? | 0                 | 7       | 10      | 74    | 21            |
|                                                 | 0.0%              | 6.3%    | 8.9%    | 66.1% | 18.8%         |
| Do you treat pregnant patients with DAAs? | 23                | 47      | 29      | 11    | 2             |
|                                                 | 20.5%             | 42.0%   | 25.9%   | 9.8%  | 1.8%          |
| Do you treat lactating patients with DAAs? | 12                | 51      | 32      | 17    | 0             |
|                                                 | 10.7%             | 45.5%   | 28.6%   | 15.2% | 0.0%          |
| Do you prescribe DAAs for children below 12 years of age? | 9                 | 35      | 53      | 10    | 5             |
|                                                 | 8.0%              | 31.3%   | 47.3%   | 8.9%  | 4.5%          |
| Do you prefer DAA over interferon therapy? | 1                 | 5       | 17      | 67    | 22            |
|                                                 | .9%               | 4.5%    | 15.2%   | 59.8% | 19.6%         |
Knowledge about genotyping and treatment of HCV

| Question                                                                 | Strongly disagree | Disagree | Neutral | Agree | Strongly agree |
|-------------------------------------------------------------------------|-------------------|----------|---------|-------|---------------|
| Do you encounter hep C cases where you prefer Interferon therapy over DAAs? | 2                 | 56       | 26      | 26    | 2             |
| Is treatment with DAAs giving more successful rate of sustained virological response (SVR)? | 0                 | 0        | 32      | 67    | 13            |
| Do you go for genotype before starting treatment with DAAs?             | 6                 | 12       | 14      | 68    | 12            |
| According to available literature genotype 3a is the most prevalent type of HCV in Pakistan. Do you come across the same? | 3                 | 1        | 22      | 56    | 30            |
| Do you thing that pan genotypic regimens eliminates the need for genotyping? | 0                 | 5        | 34      | 48    | 8             |
| Are pan genotypic combinations of DAAs easily available to the patients in our setup | 11                | 36       | 16      | 44    | 5             |

Table 3. Treatment regimens in different age groups

| Treatment Regimens | Regimens prescribed in adolescents 12-17 years of age | Regimens prescribed in adults 18 years and above without cirrhosis | Regimens prescribed in adults 18 years and above with compensated cirrhosis |
|--------------------|-------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------|
|                    | i) Sofosbuvir/ledipasvir for genotype 1,4,5,6 (12 weeks) | i) Sofosbuvir/Velpatasvir for 12 weeks                                  | i) Sofosbuvir/Velpatasvir for 12 weeks (genotype 3 for 16 weeks)           |
|                    | 0.0%                                                   | 13                                                                  | 6                                                                      |
|                    | 2.7%                                                   | 2                                                                   | 17                                                                     |
|                    | 35.7%                                                  | 40                                                                  | 45                                                                     |
|                    | 55.4%                                                  | 62                                                                  | 42                                                                     |
|                    | 6.3%                                                   | 7                                                                  | 2                                                                      |
|                    | 0.0%                                                   | 2                                                                   | 5                                                                      |
|                    | 17.9%                                                  | 27                                                                  | 31                                                                     |
|                    | 29.5%                                                  | 5                                                                   | 62                                                                     |
|                    | 42.0%                                                  | 62                                                                  | 4                                                                      |
|                    | 10.7%                                                  | 8                                                                   | 4                                                                      |
|                    | 0.0%                                                   | 27                                                                  | 5                                                                       |
|                    | 24.1%                                                  | 5                                                                   | 62                                                                     |
|                    | 4.5%                                                   | 14                                                                  | 14                                                                     |
|                    | 55.4%                                                  | 14                                                                  | 14                                                                     |
|                    | 16.1%                                                  | 14                                                                  | 14                                                                     |
|                    | 56.3%                                                  | 14                                                                  | 14                                                                     |
|                    | 18.8%                                                  | 14                                                                  | 14                                                                     |
|                    | 0.0%                                                   | 14                                                                  | 14                                                                     |

3.6 Treatment Regimens of HCV in Different Age Groups

55.4% of the physicians reported that the regimen prescribed in adolescents [12-17] is Sofosbuvir/ribavirin for genotype 3 (24 weeks), Sofosbuvir/ledipasvir for genotype 1,4,5,6 (12 weeks (55.4%) and Sofosbuvir/ribavirin for genotype 2 (12 weeks) (42%).
followed by 53.6% who were prescribing Sofosbuvir/Daclatasvir for 24 weeks. 51.8% were neutral in prescribing Sofosbuvir/Daclatasvir for 12 weeks where genotype distribution was known and Sofosbuvir/Velpatasvir for 12 weeks and 16 weeks for genotype 3 (40.2%). However, 53.6% agreed to prescribing Sofosbuvir/ Daclatasvir for 24 weeks in patients (above 18 years) with compensated cirrhosis.

4. DISCUSSION

HCV is a leading cause of liver-related mortality worldwide and was estimated to have caused 333,000 deaths in 1990, 499,000 in 2010, and 704,000 in 2013. Countries with the highest HCV prevalence (≥5%) are mainly low-middle income countries (LMIC), and include Egypt 4.4–15.0%, Gabon 4.9–11.2%, Uzbekistan 11.3%, Cameroon 4.9–13.8%, Mongolia 9.6–10.8% and Pakistan 6.8% [18]. Pakistan bears around one-tenth of the global HCV burden which is expected to rise further by 2030 [9]. The number of prevalent and newly reported HCV infected individuals is going to raise by two-thirds to 1.1 million new infections every year and near to 1.5 million individuals will not be able to survive due to ESLD [17]. Fortunately, with the arrival of new DAAs, the cure rates have reduced noticeably [19]. The treatment regimen has also been on the shift from interferons to DAAs [20]. However even after the development of these astonishing therapeutic regimens, the success in achieving the targets set by WHO are difficult to meet because of the lack of development of national strategic plan for the eradication of HCV by 2030 in most of the third world countries [21]. Sustained virologic response (SVR) is defined as the absence of detectable levels of plasma HCV RNA 12 weeks after the completion of therapy. Patients who achieve SVR have stable virologic remission over the years following treatment and experience reversal of liver fibrosis and better liver-related outcomes [22]. In our study the respondents were asked about the achievement of successful SVR with both interferon and DAAs, it is evident from our results that according to most of practitioners, treatment with DAAs gives more successful rate of SVR thus are preferred over interferon. Literature also reported similar outcomes [23]. Our results have shown genotype 3a as the most common type of genotype found in HCV infected patients which are consistent with the previous studies showing that genotype 3a is the most common type (69.1%), followed by genotypes 1 (7.1%), 2 (4.2%), and 4 (2.2%) in Pakistan [9]. Prior to 2014, HCV treatment was mainly focused on the use of interferon based regimens with generally low cure rates, longer duration of treatment and subsequent toxicity but with the advent of oral DAA they are capable of treating Hep C infection with increased rates of sustained virological response [24]. WHO in 2016 provided updated guidelines with introduction of several pangenotypic regimens which successfully resolved HCV infection in over 85% of treated patients for all six major genotypes which are approved by FDA such as sofosbuvir-velpatasvir, sofosbuvir-daclatasvir, and glecaprevir-pibrentasvir as well as sofosbuvir-ledipasvir [25]. These pan genotypic regimes according to various trials and observational studies depicted higher number of patients achieving SVR12 across genotype 1 through 4 [26]. Currently, the pangenotypic DAAs glecaprevir-pibrentasvir (8 week course), sofosbuvir-daclatasvir (12 week course), and sofosbuvir-velpatasvir (12 week course) are approved in most markets for the treatment of HCV-infected patients without cirrhosis [27]. According to our results sofosbuvir-ribavirin is the most prescribed option for genotype 3. Sofosbuvir is a nucleotide analogue which is effective against genotype 3 which is emerging as difficult to treat genotype specially if the patient enters in the phase of cirrhosis [28,29]. Various studies in this regard have reported that 12 weeks treatment with sofosbuvir and ribavirin resulted in a substantial decrease in viral RNA load leading to SVR in 92% against genotype 2 or 3 infected patients after 24 weeks treatment [27]. A single center study conducted on 100 patients reported that sofosbuvir combination with daclatasvir resulted in 94% SVR after 24 weeks of treatment [30].

5. CONCLUSION

In this study, we could see that the participants’ knowledge and practices regarding use of DAAs according to WHO guidelines, their preference over interferon therapy and recommended combinations for different age groups was appreciable, however there is still a gap of knowledge among doctors regarding treatment of HCV with DAAs which needs to be filled with the help of proper health educational programs and training.

CONSENT

As per international standard or university standard, patients’ written consent has been collected and preserved by the author(s).
ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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