Review Article **Open Access**

Meta-Analysis of the Effectiveness of Sofosbuvir-Based Regimens in Treating Hepatitis C Genotype 3

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ABSTRACT

Hepatitis C virus (HCV) is an RNA virus with seven primary genotypes. It is highly prevalent in Pakistan, especially genotype 3. HCV infection can progress to a chronic state with further complications. Direct-acting antiviral agents (DAAV) were introduced in 2014 as a treatment option, some of which include Sofosbuvir (SOF), Daclatasvir (DCV), Velpatasvir (VEL) and Ribavirin (RV). This meta-analysis was performed to outline the treatment response and efficacy of DAAV in HCV infected patients.

We systematically searched PubMed, Web of Science, MEDLINE, and Google Scholar for studies from January 2019 to December 2023. The studies selected met the criteria of patients having chronic HCV infection (genotype 3) and either compensated cirrhosis or decompensated chronic liver disease. Treatment regimens with DAAV specifically were included. The primary outcomes [sustained viral response (SVR), rapid virological response (RVR), end-of-treatment response (ETR)] were highlighted to assess treatment response.

The studies proved that the use of direct-acting antiviral agents in different combinations was very effective against HCV infection with minimal side-effects.

KEYWORDS: effectiveness, hepatitis C virus, meta-analysis, Sofosbuvir

How to cite this Article:
Siddique H, Tariq SS, Asghar SP, Fahim MF. Meta-Analysis of the Effectiveness of Sofosbuvir-Based Regimens in Treating Hepatitis C Genotype 3. J Bahria Uni Med Dental Coll. 2023;14(3):217-23 DOI: https://doi.org/10.51985/JBUMDC2024319

INTRODUCTION:

Hepatitis C is a small, single-stranded RNA virus categorized within the hepacivirus family and the Flaviviridae genus. It is comprised of seven primary genotypes (1-7), each of which contains multiple sub-genotypes.[1]

According to epidemiological data, the prevalence of hepatitis C virus (HCV) shows 71 million people affected globally with a mortality rate of 3.5-5 million deaths annually. In Pakistan, the prevalence of hepatitis C was 8.2% in 2016,2 which has decreased to 6% in 2019.[3] Province wise, the prevalence is 5.46% in Punjab, 2.55% in Sindh, 6.07% in Khyber Pakhtunkhwa, 25.77% in Balochistan, and 3.37% in federally administered tribal areas.[4] Because of the disease's great prevalence in the population, the source of disease transmission is being examined extensively in order to limit its progression. According to the literature, the hepatitis C virus is transmitted through infected blood, and common sources of spread include injections, transmission via infected blood transmission, use of infected needles and syringes, hospital transmission, and sharp instruments used in grooming as well as inadequate sterilization of medical equipment.[5-9]

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Received: 30-01-2024
Accepted: 09-07-2024 1st Revision: 24-06-2024

Hepatitis C can cause acute or chronic cirrhosis in 10-20% of cases and hepatocellular cancer in 1.5%.[10-15] In affected patients, 55-85% will progress to chronic HCV infection.[16] Genotype 3 in particular, which is most prevalent in South Asia,[17,18] is known to cause fibrosis and steatosis in some patients.[19] In Pakistan the main genotype seen is genotype 3 with an occurrence rate of 67-87%.[20,21] According to a recent study, HCV antibodies were found in 13.2 million youngsters.[22] The patients had some laboratory investigations performed during selection, such as complete blood count (CBC) and liver function tests (LFTs).

As a treatment regime, Direct-Acting Antiviral Agents (DAAV) were approved by the FDA. Compared to previous pegylated interferon therapy, DAAV proved to have a better safety profile and improved results.[23] The efficacy of these drugs was measured through sustained virological response (SVR) and rapid virological response (RVR). A review of

the last 30 years revealed that, for treatment-naive and non-cirrhotic patients, SVR rates of nearly 100% were possible with various DAA regimens; there is consensus in real-world and clinical data about GT-3, although geographical disparities in SVR rates continue.[24]

Multiple studies conducted in different areas of Pakistan highlighted some of the drugs used in the treatment of Hepatitis C and their effects on the affected patients. One of the drugs is Sofosbuvir (SOF), which works as an HCV polymerase pyrimidine analogue. In a study conducted in Pakistan, out of 162 patients, high SVR and RVR were achieved after 8 weeks of therapy. For genotype 3 specifically, 100% SVR was achieved.[25] Daclatasvir (DCV), an inhibitor of the virus also showed a good SVR according to a study conducted in Pakistan at Jinnah Hospital, Lahore.[26] Another prominent drug is Velpatasvir (VEL), a non-structural protein 5A (NS5A) HCV protein inhibitor. A combination of this drug with sofosbuvir yielded exceptional results in patients without cirrhosis according to a study conducted in Khyber teaching hospital, Peshawar[4].

Adding ribavirin to DCV and SOF also proved effective according to a study in South Punjab.[27] However, genotype 3 HCV patients showed better response compared to other genotypes. Treatment outcomes, however, also depend on patient factors such as age extent of liver disease.[28]

This meta-analysis was performed to highlight the SVR and RVR rates of DAAV in different studies conducted in Pakistan.

METHODOLOGY:

1. **Study Setting and Duration:**

Studies published between January 2019 to December 2023 were considered for review. Only the studies that were performed in a hospital setting were included. The articles included in the review had various study designs, including observational studies, cohort studies, case-control studies, and randomized controlled trials (RCTs). The outcomes and results of the studies performed were essential in providing sufficient data for this meta-analysis.

2. **Inclusion criteria:**

Studies that were conducted in Pakistan between 2019-2023 were considered for this review. The inclusion criteria consisted of:

§ Chronic HCV infection,
§ Having genotype 3,
§ Compensated cirrhosis (CC), and decompensated chronic liver disease (DCLD);
§ Intervention used (SOF + DCV, SOF + VEL, SOF, ribavirin);
§ Primary outcomes (SVR rate after either 12 or 24 weeks, RVR rate after either 4 or 8 weeks, ETR after 12 weeks);
§ Study designs (real-world studies),
§ Laboratory assessment, primarily HCV RNA PCR and others (such as: CBC, LFTs, RFTs, PT, INR, Serum Albumin, Fibro scan and Ultrasound abdomen).

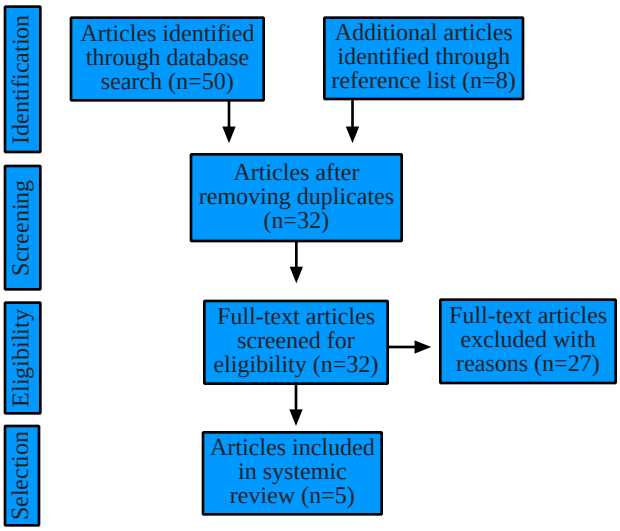
3. **Exclusion criteria:**

The studies based on the following criteria were excluded from this meta-analysis:

§ Patient with HCV infection of a genotype other than 3,
§ Patients co-infected with hepatitis B,
§ Relapsed or non-responding patients,

Patients who were treated with drugs/combination of drugs other than (SOF + DCV, SOF + VEL, SOF, ribavirin).

Flow Chart showing selection process of studies



1. **Study Participants and Treatment Regimens:**

A total of 1,054 patients were a part of all the studies combined. The age and disease status varied among all the participants. In terms of genotypes, genotype 3 was the most prevalent and it showed varying responses to different treatment regimens. Primarily, four treatment regimens were assessed: Sofosbuvir / Daclatasvir, Sofosbuvir / Velpatasvir / Daclatasvir, Sofosbuvir only, and Sofosbuvir / Daclatasvir with / without Ribavirin.

2. **Study Search and Retrieval:**

Systematic searches were conducted on PubMed, MEDLINE, Web of Science, and Google Scholar. The search was performed using specific keywords related to hospital settings, genotype and drugs used. The specified year range was confirmed, titles and abstracts were screened for relevance, and full-text articles were then obtained for further assessment.

3. **Quality Assessment:**

Each study selected for review underwent a quality assessment to evaluate its methodological rigor and potential biases. The factors considered during the assessment included study design, sample size, control for confounders, and reporting of results.

4. **Data Analysis:**

The data extracted from the selected studies were synthesized using meta-analysis techniques. To combine and analyse the data, we used a random-effects model through DerSimonian-Laird approach from JASP software. The pooled effect was calculated with a confidence interval of 95%. For heterogenicity between studies, I^2 statistics were used. The results are displayed in a forest plot.

RESULTS:

In a series of studies conducted in Pakistan between 2019 and 2023, the following significant findings have been observed in the context of hepatitis C treatment. i.e.:

§ Butt et al: Effectiveness of Sofosbuvir and Daclatasvir in treatment of Hepatitis-C: An experience of tertiary care hospital in Karachi[10]

§ Jawad et al: Safety and efficacy of Sofosbuvir therapy in chronic hepatitis C patients of Peshawar, Khyber Pakhtunkhwa[25]

§ Khan et al: Efficacy of Daclatasvir with Sofosbuvir for Treating Chronic Hepatitis C Genotype 3[26]

§ Waqas et al: Evaluation of Direct-Acting Antiviral Drugs for Hepatitis C Genotype 3 Patients from ages 30-50 years in Sialkot, Pakistan[19]

§ Younus et al: Diagnostic approach to elucidate the efficacy and side effects of direct-acting antivirals in HCV infected patients[29]

The characteristic findings in each research are presented in the following tabulated form:

In the first study, led by Butt,[10] the research unveiled an overall sustained virological response (SVR) rate of 88.3%. It's important to note that this response rate displayed variations among patients with distinct liver conditions. Specifically, those with Chronic Hepatitis C (CHC) showed a remarkable SVR of 95%, whereas patients with Compensated Cirrhosis (CC) had an 88% SVR, and individuals with Decompensated Chronic Liver Disease (DCLD) achieved an even higher SVR of 92%. Furthermore, the study reported an end of treatment response (ETR) rate of 97.33%, with variations across liver conditions as well, revealing an ETR of 98% in CHC, 98% in CC, and 95.8% in DCLD.

The second study, conducted by Jawad,[25] demonstrated notable findings with a high SVR rate of 97%. Notably, patients with genotype 3 showed exceptional results with a 100% SVR. The ETR was equally impressive at 98.7%, with 100% ETR observed in genotype 3. The study also found a rapid virological response (RVR) of 94%, with genotype 3 showing an even higher RVR of 99%. Khan's[26] study reported a SVR rate of 91.1%. Additionally, the ETR was 82.9%. It's important to note that the study examined ETR at different treatment durations, revealing an ETR of 74.8% at 4 weeks, which increased to 82.9% at 8 weeks. This suggests that treatment response rates improved with extended treatment durations.

	Place	Time	Sample Size	Study Design	Drug regimen used	Age	SVR	ETR	RVR
Butt et al	JPMC, KHI	Jan 2019 - dec 2020	300 (chc:200, Cc:51, DCLD:49)	prospective observational study	SOF/ DCV/ RV	>12 yr.	88.3% (95% in CHC, 88% in CC and 92% in DCLD) 97.9% in gen 3	97.33% (98% in CHC, 98% in CC and 95.8% in DCLD)	
Jawad et al	Khyber Teaching hospital, Peshawar.	April to June 2018	162	prospective non-randomized study	SOF	20-68 yr	97% (100% in gen 3)	98.7% (100% gen 3)	94% (99% gen 3)
Khan et al	Hepatitis Clinic, Medical Unit–II, Jinnah Hospital, Lahore	Jan 2019 to June 2019.	135	Interventional case-series study	SOF / DCV	18-80 yr	91.1%	82.9	4wks:74.8% 8wks:82.9%
Waqas et al	Sialkot, Pakistan	Issued on Dec 2022	228 (177 gen 3)	follow-up research	SOF/DCV/ VEL	30-50 yr.	90%		
Younas et al		January to August 2018	229 (216 gen 3)	prospective study	SOF/DCV	18-75 yr	93% (92.6% in gen 3)		

KEY: SVR: sustained virological response, ETR: end of treatment response, RVR: rapid virological response SOF: sofosbuvir, DCV: daclatasvir, VEL: velpatasvir, RV: ribavirin, CHC: chronic hepatitis c, CC: compensated cirrhosis, DCLV: decompensated chronic liver disease

Waqas'[19] study found an overall SVR rate of 90%, though it did not specify variations based on liver conditions or genotypes.

Lastly, Younus'[29] study reported a high SVR of 93%. Notably, patients with genotype 3 achieved a slightly lower but still impressive SVR of 92.6%.

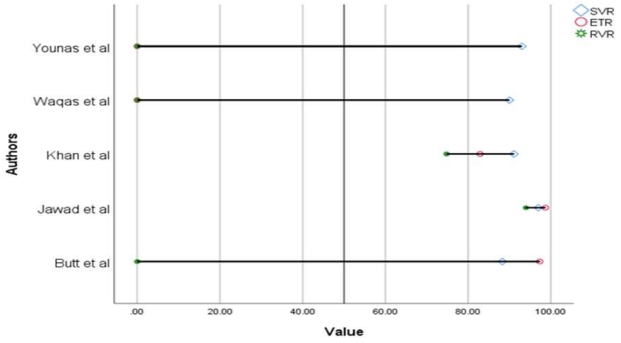
These valuable findings can be seen in the forest plot plotted below, offering a comprehensive overview of the treatment response rates.

The overall SVR was calculated to be 91.8% (95% CI: 88.53-95.23%). The I^2 statistics calculated a value of 99.9%, showing high heterogeneity among the studies.

Treatment Efficacy:

1. Sofosbuvir/Daclatasvir: The Sofosbuvir/Daclatasvir regimen achieved a mean sustained virological response (SVR) rate of 90.6% across the studies. The SVR rates ranged from 90% to 97.33%.

2. Sofosbuvir/Velpatasvir/Daclatasvir: The regimen demonstrated a mean SVR rate of 90%.



KEY: SVR: Sustained virological response, ETR: End of treatment response, RVR: Rapid virological response

3. Sofosbuvir/Ribavirin/Daclatasvir: The regimen yielded an SVR rate of 88.33%.

4. Sofosbuvir: This regimen alone yielded SVR rate of 97%.

Genotype Specificity:

Genotype 3 was the most prevalent genotype among the study participants, with varying responses to different regimens. Sofosbuvir/Velpatasvir consistently demonstrated high efficacy in treating genotype 3, with SVR rates reaching up to 90%. Sofosbuvir/Daclatasvir also showed effective outcomes against genotype 3, with SVR rate of 92.9%. Sofosbuvir regimen alone achieved SVR of 100% in genotype 3.

Genotype Specificity across various studies:

The studies offer valuable insights into the genotype-specific and overall effectiveness of different treatment regimens for hepatitis C. While genotype 3 was notably prevalent, the studies collectively demonstrated high treatment efficacy across various genotypes.

1. In the study carried out by Waqas et al a pooled SVR rate of over 90% was achieved for patients aged 30-50 with HCV genotype 3 with combination regimen of SOF/DCV/VEL.

2. In Butt et al's study, the Sofosbuvir, Daclatasvir and Ribavirin (SOF/DCV/RV) regimen exhibited an impressive 88.33% SVR rate across all genotypes, emphasizing its broad effectiveness.

3. Jawad et al's study, focusing on Sofosbuvir therapy, reported an outstanding 98.7% response rate at the end of treatment, SVR of 97% and RVR of 94%, showcasing strong overall 100% efficacy in genotype 3.

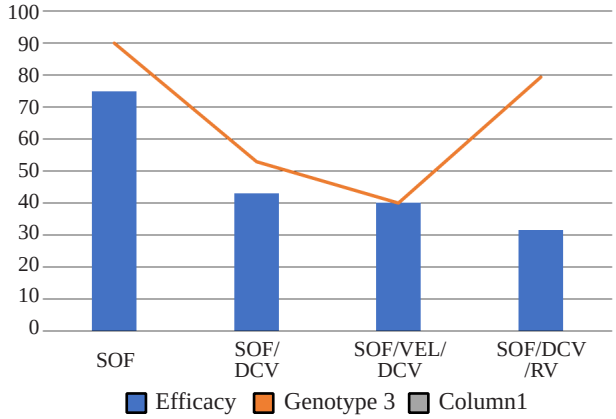
4. Moreover, Younas et al's study, revealed a substantial 93% SVR rate, with the SOF/DAC regimen demonstrating a 92.6% efficacy rate across genotype 3 with SOF/DCV.

5. While Khan et al's study revealed SVR of 91.1% across all genotypes with ETR of 82.9% with SOF/DCV regimen.

Additional insights into the overall treatment efficacy of the drug regimens employed in the studies are presented in the bar graph below. Furthermore, a dedicated line graph is provided to illustrate the specificity of these findings for genotype 3. Both graphical representations are interpreted as follows to enhance our understanding of the comparative outcomes and the genotype-specific implications of the treatments under investigation.

DISCUSSION:

Chronic HCV infection is mostly asymptomatic.[30] Hepatitis C has the potential to result in acute or chronic cirrhosis in approximately 10-20% of cases and may lead to hepatocellular carcinoma in about 1.5% of instances.[10] Notably, genotype 3, which is highly prevalent in Pakistan,[17] is recognized for its tendency to cause fibrosis and steatosis in certain individuals.[19] Recent research indicates that HCV antibodies were detected in 13.2 million young individuals.[22] During the patient selection process, various laboratory tests, including complete blood count (CBC) and liver function



KEY: SOF: sofosbuvir, DCV: daclatasvir, VEL: velpatasvir, RV: ribavirin
Y axis: Efficacy, X axis: drug regimens

tests (LFTs), were conducted**.**

Waqas et al achieved a remarkable pooled SVR rate of over 90% for HCV genotype 3 patients aged 30-50 using the SOF/DCV/VEL regimen. This impressive outcome aligns closely with the findings in study done in Year 2020 in Pakistan, which reported an overall SVR rate of 95.5%, reinforcing the consistency of the regimen's high efficacy across different studies.[31] Similarly, another study exhibited rapid viral load reduction, with 91% of patients achieving PCR negativity after four weeks, and a corresponding SVR12 rate of 85.5%, mirroring the robust results seen in the Sialkot study.[32] Moreover, another research displayed compelling efficacy, with a 98.9% end-of-treatment response and a strong SVR of 95.8%, emphasizing the regimen's potency, akin to the findings observed in the Sialkot study.[2] These parallels underscore the uniformity in outcomes and reinforce the notion that the SOF/DCV/VEL regimen consistently delivers potent results in treating HCV genotype 3 patients.

Much like the Butt et al study, which reported an impressive 88.33% SVR rate across all genotypes with the SOF/DCV/RV regimen, several other studies have produced parallel results. Another study, focusing on patients with chronic hepatitis C genotype 3, demonstrated that both SOF/RBV and SOF/DCV±RBV regimens yielded similar SVR12 rates, achieving an overall SVR of 91.9%.[33] The addition of ribavirin to the combination is also recommended by the European association for study of liver (EASL), showing its effectiveness is further supported by studies outside Pakistan as well.[34] This emphasizes the potency of these regimens in their respective contexts, mirroring the broad effectiveness observed in the Karachi study. Moreover, one other study, achieving an outstanding 98.7% response rate at the end of treatment and a 97% SVR in genotype 3 patients, reaffirms the robust performance of the SOF/DCV/RV regimen, consistent with the Butt et al study's results.[35] Furthermore, another study found that treatment with 400 mg of sofosbuvir plus 100 mg of velpatasvir for 12 weeks was both well-tolerated and highly effective, aligning with the consistent notion that these regimens offer potent and broadly effective treatment options for chronic HCV across various genotypes.[36]

The Jawad et al study reported an outstanding 98.7% response rate at the end of treatment and a robust 97% SVR in genotype 3 patients, demonstrating the high efficacy of Sofosbuvir therapy. In a parallel manner, study done in tertiary hospitals in Pakistan, showcased an impressive response to treatment, with a 95.28% SVR12 rate.[37] These results highlight the consistent findings of potent treatment options for patients with chronic HCV, particularly those with genotype 3, further affirming the efficacy of Sofosbuvir-based therapies in achieving sustained viral response.

Using a SOF-based regimen is linked to poorer outcomes (lower SVRs) in cases of advanced liver disease.[38] These patients have a higher chance of developing HCC and cirrhosis problems even after receiving therapy.[39] Even when clinical and laboratory results improve, these concerning characteristics still need to be constantly monitored.[40,41]

The Younus et al study revealed a substantial 93% SVR rate, with the SOF/DCV regimen demonstrating a 92.6% efficacy rate across genotype 3, showcasing the effectiveness of this treatment along with Khan et al, showing SVR of 91.1% with SOF/DCV therapy. In a parallel vein, study conducted in Pakistan, reported an outstanding ETR of 98.9% and a strong SVR of 95.8%, endorsing the efficacy of the Sofosbuvir and Daclatasvir combination.[35] Additionally, another study conducted in 2020 highlighted a noteworthy overall SVR rate of 95.5%.[31] Patients who progressed to liver fibrosis as a result of HCV also showed regression with this combination therapy according to the results of another study.[42]

Regarding side-effects, a study conducted in Lahore, Pakistan reported fatigue, arthritis, headache, loss of appetite and anemia in patients undergoing therapy. However, it also noted that patients who were taking a combination of Sofosbuvir and Velpatasvir experienced more side effects compared to patients on Sofosbuvir and Daclatasvir combination.[43] When compared to the previous regimen of interferon therapy, the side-effects were significantly lesser overall of direct-acting antiviral drugs.[44]

CONCLUSION:

The combined results of these studies conclude that direct-acting antiviral agents, particularly the SOF/VAL and SOF/DCV regimens, were very effective and had good safety profiles in chronic Hepatitis C virus infection. Genotype 3, particularly common in Pakistan, showed great response to the drugs. The results conclude that choosing not only the appropriate agents but setting the correct regimen is vital for the best possible treatment that can be achieved against Hepatitis C infection in Pakistan. All the findings are valuable in the ongoing attempt to curb the prevalence of the disease in this region.

Authors Contribution:
Hafsa Siddique: Conceptualization, planning, synopsis writing, literature search, and manuscript writing
Syed Sufyan Tariq; Conceptualization, planning, synopsis writing, literature search, and manuscript writing
Syed Parvez Asghar: Conceptualization, planning, synopsis writing, literature search, and manuscript writing
Muhammad Faisal Fahim: Conceptualization, planning, synopsis writing, literature search, and manuscript writing.

REFERENCES:

01. Negro F, Alberti A. The global health burden of hepatitis C virus infection. Liver Int. 2011 Jul;31 Suppl 2:1–3 DOI:10.1111 /j.1478-3231.2011.02537.x.

02. Ahmed T, Ahmad OHA, Bilal M, Alam S, Zaheer S, Gul Z. Comparison of Efficacy of Sofosbuvir & Daclatasvir with Sofosbuvir and Velpatasvir in Achieving SVR in Patients of Chronic Hepatitis C with Genotype 3. Pakistan Journal of Medical & Health Sciences. 2022 Jun 25;16(04):1155–1155 DOI:10.53350/pjmhs221641155.

03. HaqqiAleena, MunirRimsha, KhalidMuhammad, KhurramMuhammad, ZaidMuhammad, AliMuhammad, et al. Prevalence of Hepatitis C Virus Genotypes in Pakistan: Current Scenario and Review of Literature. Viral Immunology [Internet]. 2019 Nov 7 [cited 2023 Oct 15]; DOI:10.1089/vim.2019.0058. Available from: https://www.liebertpub. com /doi/10.1089/vim.2019.0058

04. Shah I, Ahmad W, Qadir A, Muhammad I, Islam M, Shah M, et al. Efficacy and Safety of Sofosbuvir and Velpatasvir Combination for the Treatment of Chronic Hepatitis C in Patients With or Without Cirrhosis. Cureus [Internet]. 2021 Nov 20 [cited 2023 Sep 21]; DOI:10.7759/cureus.19768.

05. The epidemiology of hepatitis C virus in Pakistan: systematic review and meta-analyses | Royal Society Open Science [Internet]. [cited 2023 Oct 28]. Available from: https://royalsociety publishing .org/doi/full/10.1098 /rsos. 180257

06. Abbas: Prevalence and mode of spread of hepatitis... - Google Scholar [Internet]. [cited 2023 Oct 28].

07. Aslam: Association between smallpox vaccination and... - Google Scholar [Internet]. [cited 2023 Oct 28].

08. High prevalence of hepatitis C virus infection in the largest province of Pakistan - IDREES - 2008 - Journal of Digestive Diseases - Wiley Online Library [Internet]. [cited 2023 Oct 28].

09. Hashmi A, Saleem K, Soomro JA. Prevalence and Factors Associated with Hepatitis C Virus Seropositivity in Female Individuals in Islamabad, Pakistan. Int J Prev Med. 2010;1(4): 252–6.

10. Butt N, Anoshia, Khan MA, Akbar A. Effectiveness of Sofosbuvir and Daclatasvir in treatment of Hepatitis-C: An experience of tertiary care hospital in Karachi. Pak J Med Sci. 2021;37(7):2014–9 DOI:10.12669/pjms.37.7.4627.

11. Moussalli J, Opolon P, Poynard T. Management of hepatitis C. Journal of Viral Hepatitis. 1998;5(2):73–82 DOI:10.1046/j.1365-2893.1998.00086.x.

12. Seeff LB. Natural history of viral hepatitis, type C. Semin Gastrointest Dis. 1995 Jan;6(1):20–7.

13. Bisceglie AMD. Hepatitis C and Hepatocellular Carcinoma. Semin Liver Dis. 1995;15(1):64–9 DOI:10.1055/s-2007-1007263.

14. An Assay for Circulating Antibodies to a Major Etiologic Virus of Human Non-A, Non-B Hepatitis | Science [Internet]. [cited 2023 Oct 28]. Available from: https://www.science.org /doi/abs/10.1126/science.2496467

15. Hepatitis C Virus Infection | NEJM [Internet]. [cited 2023 Oct 28]. Available from: https://www.nejm.org/doi /full/10.1056/nejm200107053450107

16. Riaz HA, Nishwa DE, Fatima A, Wahid B, Ali A, Kumari B, et al. Risk of adverse outcomes following treatment with direct acting antiviral drugs in HCV infected patients with liver cirrhosis. Heliyon [Internet]. 2023 May 1 [cited 2023 Oct 16];9(5) DOI:10.1016/j.heliyon.2023.e16169.

17. Khan A, Nadir A, Mushtaq MH, Junaid K, Khan AM, Ali H, et al. Molecular epidemiology and genotype distribution of hepatitis C in Pakistan; a multicenter cross-sectional study. Infection, Genetics and Evolution. 2020 Oct 1;84:104372 DOI:10.1016/j.meegid.2020.104372.

18. Ramia S, Eid-Fares J. Distribution of hepatitis C virus genotypes in the Middle East. International Journal of Infectious Diseases. 2006 Jul 1;10(4):272–7 DOI:10.1016/j.ijid. 2005.07.008.

19. Waqas K, Saddiqa A, Naqvi SZH, Qureshi JA, Dar OA, Butt MS, et al. Evaluation of Direct-Acting Antiviral Drugs for Hepatitis C Genotype 3 Patients from ages 30-50 years in Sialkot, Pakistan. 2022;18(12).

20. Shah HA, Jafri W, Malik I, Prescott L, Simmonds P. Hepatitis C virus (HCV) genotypes and chronic liver disease in Pakistan. J Gastroenterol Hepatol. 1997 Nov;12(11):758–61 DOI:10. 1111/j.1440-1746.1997.tb00366.x.

21. Idrees M, Riazuddin S. Frequency distribution of hepatitis C virus genotypes in different geographical regions of Pakistan and their possible routes of transmission. BMC Infect Dis. 2008 May 23;8:69 DOI:10.1186/1471-2334-8-69.

22. Bakr AA, Sarwar S, Aslam N, Ghias M, Mehfooz I. Sofosbuvir-Velpatasvir for Chronic Hepatitis C Virus-Infected Children and Young Adults: Efficacy and Safety. Annals of King Edward Medical University. 2023 Sep 2;29(2):118–22 DOI:10.21649 /akemu.v29i2.5433.

23. Munir N, Bajwa H, Aftab M, Bibi A, Mahmood Z, Shoukat M, et al. Safety Status of Interferon-free All-oral Direct-acting Antiviral Agents (DAAs) to treat HCV patients in Tertiary Care Hospital of Faisalabad-Pakistan. 2023 May 4;93–100 DOI:10.52587/njhms.v3i2.26.

24. McPhee F. Developments in the treatment of HCV genotype 3 infection. Expert Review of Anti-infective Therapy. 2019 Oct 3;17(10):775–85 DOI:10.1080/14787210.2019.1676730.

25. Jawad M, Attaullah S, Khan S, Ullah F, Zahid M, Saeed F, et al. Safety and efficacy of Sofosbuvir therapy in chronic hepatitis C patients of Peshawar, Khyber Pakhtunkhwa, Pakistan. Songklanakarin Journal of Science and Technology. 2022 Jul 18;44:683–9 DOI:10.14456/sjst-psu.2022.93.

26. Khan FA, Ahmad M, Khan I, Khan AAT, Kashif M, Malik T. Efficacy of Daclatasvir with Sofosbuvir for Treating Chronic Hepatitis C Genotype 3. Pakistan Journal of Medical & Health Sciences. 2022 Jun 1;16(05):240–240 DOI:10.53350/ pjmhs22165240.

27. Malghani WS, Chaudhary FMD, Shahid M, Tameez-ud-din A, Malik R, Din ATU. Safety and Efficacy of Daclatasvir with Sofosbuvir and Ribavirin in Hepatitis C Virus Infection: A Real World Experience from South Punjab,DOI:10.1101/ 2021. 10.23.21265410.

28. Haider SA, Ahmad B, Ali S, Haider A, Bashir S, Mahmood N. Sofosbuvir and Ribavirin Combination Therapy Response in Various Hepatitis C Virus Genotypes in Peshawar, Khyber Pakhtunkhwa. Jundishapur J Microbiol [Internet]. 2020 [cited 2023 Oct 16];13(6) DOI:10.5812/jjm.99625.

29. Younas S, Mukhtar H, Gohar UF, Alsrhani A, Alzahrani B, Junaid K, et al. Diagnostic approach to elucidate the efficacy and side effects of direct-acting antivirals in HCV infected patients. The Journal of Infection in Developing Countries. 2021 Oct 31;15(10):1489–96 DOI:10.3855/jidc.12912.

30. The natural course of HCV infection and the need for treatment [Internet]. [cited 2023 Oct 16].

31. Mushtaq S, Akhter TS, Khan A, Sohail A, Khan A, Manzoor S. Efficacy and Safety of Generic Sofosbuvir Plus Daclatasvir and Sofosbuvir/Velpatasvir in HCV Genotype 3-Infected Patients: Real-World Outcomes From Pakistan. Frontiers in Pharmacology [Internet]. 2020 [cited 2023 Oct 15];11.

32. Akhter TS, Umar M, Khaar H-T-B, Aslam F, Nisar G, Naseer A, et al. Sofosbuvir For The Treatment Of Hepatitis C Genotype 3 Infected Patients In Pakistan. Journal of Ayub Medical College Abbottabad. 2017 Feb 1;28(4 Sup):884–9.

33. Sarwar S, Tarique S, Aleem A, Khan AA. Effect of adding daclatasvir in sofosbuvir-based therapy in genotype 3 hepatitis C: real-world experience in Pakistan. European Journal of Gastroenterology & Hepatology. 2019 Aug 1;31(8):1035–9 DOI:10.1097/MEG.0000000000001376.

34. EASL Recommendations on Treatment of Hepatitis C 2016. Journal of Hepatology. 2017 Jan 1;66(1):153–94 DOI:10.1016/j .jhep.2016.09.001.

35. Ullah Z, Khan SZ, Khan H, Lodhi H. Efficacy of sofosbuvir and daclatasvir in achieving the end treatment response and sustained viral response in patients infected with hepatitis C Virus Genotype. Pakistan Armed Forces Medical Journal. 2022;72(3):1074–7.

36. Pianko S, Flamm SL, Shiffman ML, Kumar S, Strasser SI, Dore GJ, et al. Sofosbuvir Plus Velpatasvir Combination Therapy for Treatment-Experienced Patients With Genotype 1 or 3 Hepatitis C Virus Infection. Ann Intern Med. 2015 Dec;163(11):809–17 DOI:10.7326/M15-1014.

37. Sohail Hussain M, Sm Qamrul Arfin M, Imtiaz Begum M, Syed Ali Raza M, Tauseef Ahmed M, Jamil Muqtadir M. Efficacy Of Sofosbuvir In Combination With Daclatasvir For The Treatment Of Hepatitis C Genotype 3a Patients In A Tertiary Care Center In Pakistan. J Popl Ther Clin Pharmacol. 2023 Sep 30;30(17):2219–24 DOI:10.53555/jptcp .v30i17 .2963.

38. Advanced liver fibrosis effects on the response to sofosbuvir-based antiviral therapies for chronic hepatitis C - Morio - 2018 - Journal of Medical Virology - Wiley Online Library [Internet]. [cited 2023 Oct 28].

39. Follow-up of sustained virological responders with hepatitis C and advanced liver disease after interferon/ribavirin-free treatment - Kozbial - 2018 - Liver International - Wiley Online Library [Internet]. [cited 2023 Oct 28

40. Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016 Sep 14;22(34):7824–40 DOI:10.3748/wjg.v22.i34.7824.

41. Kanwal F, Singal AG. Surveillance for Hepatocellular Carcinoma: Current Best Practice and Future Direction. Gastroenterology. 2019 Jul 1;157(1):54–64 DOI:10.1053/j .gastro.2019.02.049.

42. Mari A, Khoso MM, Saeed A, Ahmed S, Mari K, Hussain R. Determination of Real-world Single-center Experience with Direct-acting Antivirals for Improvement of Liver Fibrosis after Chronic Hepatitis C Treatment. Journal of Pharmaceutical Research International. 2022 Feb 23;28–35 DOI:10.9734/jpri/ 2022/v34i14B35680.

43. Kazmi S, Farooqi H, Sohail U, Zaidi SH, Majeed N, Firdus S. Sustained virological response (SVR) and safety of two direct acting anti-viral (DAA) combination therapies in Chronic Hepatitis-C infected patients of Lahore, Pakistan. A Randomized Controlled Trial: SVR and DAA Therapies in Hepatitis-C Infected Patients. Pakistan Journal of Health Sciences. 2022 Nov 30;135–9 DOI:10.54393/pjhs.v3i06.294.

44. Sajjad SF, Ahmed W uddin, Alam SE. Sofosbuvir and Ribavirin in Chronic Hepatitis C Virus Patients with No Response or Relapse with Interferon Therapy. Journal of the Dow University of Health Sciences (JDUHS). 2020 Dec 17;14(3):139–43 DOI:10.36570/jduhs.2020.3.856.