SHORT COMMUNICATION

ISSUES PERTAINING TO DAAS

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With the discovery of DAAs, the treatment of hepatitis C has improved a lot. But in this new era of DAAs several issues are also emerging. In this brief communication, we have tried to address the salient issues regarding DAAs.

Keywords: Direct acting antivirals; Resistance; Drug Interactions; Side Effects

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1. Hepatitis C viral resistance to DAAs

HCV has a high replication rate leading to low proof-reading capacity of HCV RNA dependent RNA polymerase.[1,2] This leads to a high genetic variation even within a single genotype.[3] Thus an individual infected with HCV has infect a mixture of genetically resembling strains of HCV, with a predominant wild type strain that is drug sensitive (detectable at the start of therapy) and low levels of resistant strains (not detectable at start of therapy). These resistant strains had a mutant amino acid that either makes the DAA less susceptible or makes the virus more fit.[4]

As the treatment starts with DAAs there is a rapid decline in the sensitive variant making the HCV RNA quantitative analysis negative. If the duration of DAA therapy is long enough at the end of treatment the sensitive strains are cleared leaving behind the resistant variant at low undetectable levels so the HCV RNA quantitative analysis are still negative.

As the treatment stops the change in competitive environment (vanishing of sensitive type) leads to the emergence of resistant strain causing DAA relapse/failure.

Different resistant associated strains are well documented for different DAAs with variable prevalence. E.g. Common resistant associated variants for Sofosbuvir are L159F, V321A, S282R. No data available for 1st 2 variants whereas the 3rd variant has low resistance with a prevalence of about 0.4%. Daclatasvir has a high resistance variant M28 with a prevalence of 0.5–4%. Ledipasvir has 2 high resistance variants with one of them having up to 100% prevalence for genotype 2 and 4.[5]

As a whole resistance for NS3-4A protease inhibitors like Boceprevir and Telapravir disappears from peripheral blood within few weeks to months whereas resistance to NS5A inhibitors, i.e., Daclatasvir, Ledipasvir and Ombitasvir persists for years[4] The highest barrier for resistance is amongst NS5B nucleoside polymerase inhibitors including Sofosbuvir.[5]

The DAA resistance is an upcoming issue that needs further evaluation. Pre-treatment resistant studies seem to be a part of recommendations in near future. Currently AASLD 2016 updated guidelines recommend NS5A resistance evaluation in DAA failure patients especially before considering Elbasvir/Grazoprevir for genotype 1a patients.[6] Apart from genotype 1a, NS5A resistance is also very common in genotype 3, which is more prevalent in Pakistan. A recent study by Johannes Vermehren *et al* showed an overall 39% RAVs in genotype 3 patients and 32% out of them were having NS5A resistance.[7] More insight is required while dealing with DAA failure patients in Pakistan and these patients especially with advanced fibrosis may need reinforcement of therapy with sofosbuvir/velpatasvir.[8,9] HCV resistance to DAAs can prevent patients from achieving SVR and any patient with DAA failure should be dealt according to recommended guidelines.

2. Effectiveness of Generics in the treatment of HCV infection

With the approval of new and new DAAs, there are expectations that these medications will provide effective, safe and cheap treatment for HCV. Although there is dramatic diversity in the price of generics around the globe but Hill *et al*. in 2013 pointed out that the original manufacturing cost of these DAAs is very low e.g. sofosbuvir 12-week treatment course costs approximately $ 101 and daclatasvir 12 weeks' course costs $ 20 respectively.[10]

Several generic manufacturers are available currently and the competition amongst them is causing the reduction in prices of these DAAs. Low income countries like Pakistan, Egypt, Indonesia and India have access to low cost, active pharmaceutical ingredients but their quality assurance is questionable. WHO has evolved a mechanism to arrange quality assurance of these drugs through their prequalification program.[11]

Freeman *et al* in a study of 448 patients using generic DAAs showed a SVR4 of about 94%.[12] Data from our own centre using generics as well showed ETR of 94% and SVR12 of 82% respectively.[13]

3. Is IFN still needed in the presence of DAAs?

No doubt IFN has been the mainstream drug in the treatment of HCV in recent past however its large number of disadvantages and introduction of safe and effective alternatives in the form of DAAs has limited its use and IFN may be obsolete for the treatment of HCV in near future. There is no medical reason to withhold DAAs for HCV treatment but in low income countries especially in Asia Pacific region their

penetration is very slow. So currently the only indication to IFN based therapy is no access to DAAs. Another argument in favour of IFN is the relatively better response of Asian population partly because of IL28B allele but still global viral eradication is not possible with IFN based regimens. The access to DAAs is the main issue that should be addressed. Effort of Gilead in providing its medication to 90 lowest GDP countries is an appreciable step in this regard.

4. Drug-Drug Interactions[14–19]

As with the advent of new DAAs several patients who were initially treatment ineligible because of comorbidities can now be offered therapy. Therefore, another important issue is drug-drug interactions as a lot of patients are using poly-therapy due to non-HCV issues. It is a complex subject and is difficult to cover all interaction here, but we have tried to give a bird eye view for quick reference in table-1

5. Safety of DAAs

5.1. Side Effects:

Several studies have evaluated the side effect profile of DAAs and found them to be relatively safe and well tolerated. Most of the side effects are due to Ribavirin. Commonly documented side effects in clinical trials are fatigue, headache, insomnia, itching, photosensitivity, nausea and diarrhoea and only 1–2% left treatment due to side effects.[20] The salient side effects along with their management[21–22] are tabulated in table-2.

Table-1: Drug-Drug interactions of important pharmacological agents with commonly used DAAs

	SOF	DCV	LDV	Velpatasvir
Statins	No Interaction	Dose Adjustment	Dose Adjustment but Rosuvastatin should be avoided	Only Rosuvastatin dose adjustment required. Not to exceed 10 mg
Amiodarone	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Digoxin	No Interaction	Dose Adjustment	Dose Adjustment	Clinical monitoring
Clopidogrel	No Interaction	Dose Adjustment	No Interaction	
Warfarin	No Interaction	No Interaction	No Interaction	No Interaction
Beta blockers	No Interaction	No Interaction	No Interaction	No Interaction
Ca Channel blockers	No Interaction	Dose Adjustment	Dose Adjustment (Nifedipine: no interaction)	No Interaction
ARBs/ACEI	No Interaction	No Interaction	No Interaction	No Interaction
Anti-Psychotics & Anti-Depressents	No Interaction	No Interaction	No Interaction	No Interaction
Azathioprine, Etanercept or Mycophenolate mofetil	No Interaction	No Interaction	No Interaction	No Interaction
Cyclosporine and Tacrolimus	No Interaction	No Interaction	Dose Adjustment	No Interaction
PPIs	No Interaction	No Interaction	Low single dose of PPI co-administered with drug	Low dose PPI, VEL should be taken with food
Phenytoin, Phenobarbital, Carbamazepine, Oxcabazepine		Contraindicated	Contraindicated	Contraindicated
Rifampin, Rifabutine, Rifapantine		Contraindicated	Contraindicated	Contraindicated

Table-2: DAAs related side effects and their management

Side Effect	Management
Fatigue	1. 10-15 minutes' light exercise 2. Short naps of 20 minutes during day time 3. 8-10 glasses of water/day 4. Alter work schedule
Headache	1. Take adequate fluid & rest 2. Stay in dim light 3. Acetaminophen
Insomnia	1. Maintain regular sleep cycle 2. Avoid caffeine (tea, coffee, soda, chocolate) 3. A glass of warm milk before bedtime 4. Ribavirin at about 5 pm instead of before bedtime 5. Diphenhydramine if recommended by physician
Rash, itching & Photosensitivity	1. Avoid sun exposure 2. Moisturizing lotions and soaps 3. Prefer rubbing instead of scratching 4. Apply petroleum jelly
Nausea & Vomiting	1. Ribavirin with food 2. Small, frequent meals 3. Ant-acids and anti-emetics
Diarrhoea	1. Take more fibre 2. Avoid spicy/acidic foods 3. Avoid dairy products for 2-3 days once diarrhoea resolves 4. Loperamide as advised by physician

5.2. Pregnancy & Lactation:

No DAAs are yet recommended in pregnancy and lactation. As Ribavirin is completely contraindicated in pregnancy and with the availability of Ribavirin free regimens it is expected that a pregnancy safe combination will be available soon. Although no human data is available yet in this regard but available animal models suggest SOF, LDV and Ombitasvir/Paritaprevir/Ritonavir combination to be safe for foetus. Rather Ombitasvir/Paritaprevir/Ritonavir combination has been included in category B but all the recommended regimens advocate their use with ribavirin limiting its use during pregnancy. Further studies and combinations may soon lead us to a safe alternative for women with child bearing age group.[23]

5.3. Extreme Ages:

Safety data in adults encouraged the use of DAAs in adolescents and older patients. Pharmacokinetics of sofosbuvir and ledipasvir/sofosbuvir has been evaluated in children from 12–17 year age group and comparable results have been established in this age

group[24] but still recommendations are awaited for the use of DAAs in children.

Tania Welzel *et al* presented a data of 506 elderly patients age >70 years amongst which only 5 patients discontinued therapy prematurely. 95.8% achieved SVR12 and the results were similar to other age groups.[25]

5.4. Warnings:

During a period of 31 months, 24 cases have been reported to FDA in which patients using DAAs have reactivation of Hepatitis B infection. Therefore, FDA have issued a warning for all health care providers to screen for HBV co-infection before treating HCV with DAAs and extensive monitoring for HBV flares is required during and after therapy.[26]

WARNING!!!
FDA has announced a warning for all DAA users for the possible flare of HBV co-infection

5.5. Severe Adverse Events:

As the patients with cirrhosis are now amenable to DAA therapy, a new debate has been provoked. There are few case reports that patients achieving SVR with DAAs have decompensated during or just after therapy.[27,28]

This decompensation was really due to DAAs or it was just coincidental with the natural course of the disease, needs further evaluation. The mechanism for Drug induced liver injury (DILI) using DAAs is unknown. Weather it is idiosyncratic response, altered metabolism of the drug by already damaged liver or some genetic features are involved, still needs to be established.

Maria Reig *et al* cautioned an unexpected high rate of HCC recurrence in patients achieving SVR with DAAs.[29]

These reported events are mere case reports or limited data, and further research will prove any positive relationship with the DAAs. Physicians around the world should keep these possibilities in mind and should promptly report the adverse events to FDA.

6. HCV treatment by non-specialist practitioners

With all oral DAAs, the treatment of HCV seems to be very easy with limited assessment. As HCV prevalence is very high in Pakistan and certified hepatologists and gastroenterologists are limited, so flexibility is required in this regard. Sarah Kattakuzhy conducted the ASCEND trial to determine the safety of HCV related DAA therapy by non-specialist practitioners and found it equally safe and effective.[30] Although the results are encouraging but keeping in mind our local scenario, some modifications and limitations should be implemented. Like proper training of general practitioners, encouraging them to follow the guidelines and timely referral for complications and special populations.

7. What is an ideal drug for chronic Hepatitis C? Are we expecting more DAAs in near future?

Several treatment regimens are in clinical developmental stage and could be a part of recommendations in near future. There is a continuous surge for ideal drug or combination that should be pangenotypic with excellent potency and a high barrier to resistance. Efforts are being made to look for such an ideal drug at a cheap rate. One such effort is by Drugs for neglected diseases initiative(DNDi) that in collaboration with an Egyptian pharmaceutical company which is the licensing partner of Biotech Presido Pharmaceutical California. They have developed a drug Ravidasvir and a phase III trial on 300 Egyptian patients in combination with Sofosbuvir showed 100% results in non-cirrhotic patients.[31] DNDi is now carrying out another trial in Malaysia and Thailand on 1000 patients. DNDi's agreement with the pharmaceutical company in March 2016 is expected to launch the combination therapy at a price less than $ 294 for the complete course.[32] Several other new DAAs like ABT-493, ABT-530, MK-8408, MK-3682 and GS-9857 are showing nearly up to 100% SVR12 in clinical trials.[33] With each new drug opens a whole new horizon.

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