DISCUSSION

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV). ***(Ryan and Ray, 2004)*** The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years.

In some cases, those with cirrhosis will go on to develop liver failure, liver cancer or life-threatening esophageal and gastric varices. ***(Ryan and Ray, 2004)***

HCV is spread primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment and transfusions. An estimated 130–200 million people worldwide are infected with hepatitis C. ***(Gravitz, 2011)***

The existence of hepatitis C (originally "non-A non-B hepatitis") was postulated in the 1970s and proven in 1989. ***(Wilkins, et al., 2010)*** Hepatitis C only infects humans and chimpanzees (***Davis GL, 2011).***

The virus persists in the liver in about 85% of those infected. This persistent infection can be treated with medication: at the time of the study, the standard therapy was a combination of peginterferon and ribavirin. Overall, 50–80% of people treated are cured.

Those who develop cirrhosis or liver cancer may require a liver transplant. Hepatitis C is the leading cause of liver transplantation, though the virus usually recurs after

transplantation. ***(Ray, et al., 2009)*** No vaccine against hepatitis C is available.

Egypt has the highest HCV antibody prevalence in the world nearly14.7% of Egyptian population. ***(Alter, 2007)*** The start of the epidemic is attributed to insufficiently sterilised intravenous injections during the mass anti-schistosomiasis treatment campaigns in rural areas during the 1970s. **,** ***(Frank, et al., 2000)***. Spread of HCV has therefore been studied mainly in rural areas. An early survey documented HCV clustering among households of individuals with history of parenteral treatment for schistosomiasis. ***(Rao, et al., 2002)*** More recently, in cohort studies of rural areas of Egypt, having an anti-HCV-positive family member was the strongest predictor for incident HCV infection, after adjustment for iatrogenic and community exposures. ***(Mohamed, et al,. 2005)*** Also, a mathematical model estimated that within HCV-infected couples, 6% would have acquired their infection from their partners. ***(Magder LS, et al., 2005)***

Treatment of chronic HCV genotype 4 infection in Egypt was depending on acombination of peg interferon and ribavirin but recently adirectly acting anti viral drug sofosbuvir will be add to this regimen to improve treatment out comes

In this retrospective cross section study we had followed one hundred HCV+ve (Genotype 4) Egyptian patients retrospectivly during their treatment by a combination therapy of peg interferon and Ribavirin at the out patient hepatology clinic of almebara hospital at kafr eldawar city, al behira

governorate between May 2011and May 2012 in the different stages of treatment by the following parameters at (0-3-6-12-18) months of treatment:

- PCR
- ALT, AST
- S.billrubin (total or direct)
- s.alkaline phosphatase
- TSH
- C.B.C at (0W-2W-4W-and then every 8 weeks till the end of therapy as regard hemoglobin level- total WBC count and-the platelet count.

Our study aimed at the following:

1. To determine the response of our Egyptian HCV+ve genotype 4 patients to the interferon / ribiavirin regimen for 48W and to determine cases that achieved S.V.R
2. To determine if there is significant changes in the mentioned parameters in each response group during the different stages of treatment.
3. To determine the common side effects of such regimen in our Egyptian patients and their frequencies.
4. To determine the group of patients that had stopped treatment prematurely and the causes of such stoppage.

Demographically our study was conducted to one hundred Egyptian HCV+ve (genotype 4) patients who were already candidates for peg Inf/Ribavirin regimen of which a 68 male

and 32 females and their ages ranges from a minimum of 22 years old to 58 years old with a mean age of 45.5years old.

As regard the response to treatment our study revealed that 71 cases (71%) of the study cases had achieved a S.V.R, of them a 46 males and 25 females with percentages of 64.8% males and 35.2% females of all the 71 cases that had achieved a S.V.R.it is significant that the S,V,R response is significantly higher among male patients than female patients.

Our study also revealed 11 cases (11%) of relapse of which 9 cases (81.8% of the relapsed cases) were males and 2 cases (18.2% of the relapsed cases) were females, also the relapse rate is significantly higher in males than females

Our study revealed 7 cases (7%) that are non responders (7% of all study cases) of which 5 cases (71.4% of non responders) were males, and 2 cases (28.6% of non responders), were females, also the non responding males were significantly higher than non responding females.

Our study revealed a 4 cases of break through, 3 cases males and 1 female case with a percentages of 75%males and 25%females of all cases with break through. Of all cases of break through, 3 cases the breakthrough was discovered at 6m of treatment and one case at 9m of treatment, also breakthrough was significantly higher in males

Other studies that studied the response of HCV4 patients to peg interferon and ribavirin therapy are:

- S.M. Kamal et al 2005.
- El Zayadi et al 2002.
- RMoucari et al.,2009

☒ Moucari et al 2009 aimed at studying the insulin resistance and geographical origin as a major predictors of liver fibrosis and response to peg inf/ Rib treatment in HCV +4 patient.

Where of 108 HCV4 patients 55% achieved S.V.R after 48w course of treatment.

☒ Kamal et al 2005 aimed at comparing the efficacy and safety of 24,36,48 weeks of peg inf/ Rib therapy in chronic HCV4.

Where of 287 patients 96 patients were followed for 48 weeks of treatment and S.V.R at 48 weeks was 69%.

☒ El Zayadi et al 2002 aimed at comparing the efficacy of 24,48 weeks of peg inf/Ribvirin therapy in HCV4 where S.V.R rates at 48weeks where 55%.

As regard the age of patients in relation to their response to therapy cases that achieved S.V.R had the lowest ages ranging from 22-58 years old with a mean age of 44.9. cases that were non responder and has the higher ages ranging from 40-58 years old with a mean age of 47.5, cases of breakthrough had ages from 36-55 years old with a mean of 47.0, and cases of relapse ranges from (33-58) with a mean age of 46.6.

As regard the changes in the studied parameters during different stages of treatment our study revealed the following:

As regard the changes in the previously mentioned parameters along the course of treatment, our study studied these changes in each group separately (S.V.R- non responders –Break through- relapses).

But first we should mention the basal levels of these parameters as follows:

- PCR (iu/ml) ranged from 0.007-9300.x10^6 with a mean of 160.6x$10^{6.}$
- ALT (u/l) 12-183with a mean of 59.14
- AST (u/l) 10-150 with a mean of 93.9
- Total billrubin (mg/dl) 0.08-1.30 with a mean of 0.91
- Direct billrubin (mg/dl) 0.01- 0.51 with a mean of 0.10
- ALP (u/l) 52-290 with a mean of 103
- TSH (mu/l) 0.30- 5.70 with a mean of 1.9
- HB (g/dl) 10-15 with a mean of 13.4
- PLT(X10^9/l) 89-799 with a mean of 215
- WBC (X10^9/l) 2.8-12.5 with a mean of 6.47

As regard the group that had achieved S.V.R:

1. PCR: PCR is negative in 66 cases (66%) at 3m and 5 cases PCR had decreased by 2 or more logs from the base levels at 3m and then in all negative at 6m-12m-18m.
2. ALT: our study revealed a statistically significant increases in the serum ALT at 3m compared to the basal level, at 6m there is statistically insignificant decreased in the serum ALT when compared to its level at 3m, at 12m there is

statistically significant decrease in the serum ALT when compared to both basal level and its level at 6m, at 18m there was also statistically significant decreases in the serum ALT as regard both basal level and level at 12m.

3. AST: our study revealed statistically significant increases in the serum AST at 3m when compared to its basal level, at 6m there is statistically significant decrease in the serum AST as compared to both basal level and its level at 3m,at 12m, 18m our study revealed a statistically significant decrease in the serum AST as compared to both the basal level and levels at 6m.
4. Total bilirubin: Our study revealed a statistically significant increases in the serum bilirubin at 3m when compared to it's basal level, also the study revealed a statistically significant increases in the T. billrubin when compared to the basal level or the previous level at 6-12-18m (significant increases in T-bilirubin along the course of treatment).
5. Direct bilirubin: a 3m there is insignificant decrease, with statistically significant increases in 12 and 18 m when compared basal level.
6. ALP: there is statistically insignificant increases at 3m, statistically insignificant increases at 18m when compared to basal level.
7. TSH: there is statistically insignificant increases at 3m compared to basal level, and statistically significant increases at 6m and 12m, and statistically insignificant increases at 18m.

8. HB: there is statistically significant decreases in the HB level at 2w,4w,12w,18w,20w when compared to basal level with statistically insignificant increases at 36w, statistically significant decreases at 44w also when compared to the basal level. There is statistically significant decreases in HB level at 4w, 12w, when compared by the pervious stages, and statistically significant increases at 20w, 28w when compared to previous stages and statistically in significant increases at 36w-and 44w but levels still below basal levels.
9. Platelets count: there is statistically significant decreases at stages 2w,4w,12w,20w,28w with statistically insignificant increases at 36w-44w as compared to basal level and statistically insignificant decreases at 4w,12w,20w when compared to each other and statistically significant increases at 28w when compared to 20w, and statistically insignificant increases 36w and at 44w but levels still below basal level.
10. WBC count: there is statistically significant decreases at 2w,4w,12w,20w,28w,36w,44w when compared to basal level but statistically significant increases at 28w,36w,44w when compared to previous stages when there was statistically significant decreases at 2w,4w,12w,20w. End of treatment levels are still below basal level.

As regard the relapse group:

1. PCR: there was a +ve detectable levels of PCR viral load discovered at 18m.

2. ALT, AST: There are statistically significant increases in the serum levels at 18m when compared to basal levels.
3. T. bilirubin: there is statistically significant increase at 12m,18m when compared to basal levels.
4. D. bilirubin: there is statistically insignificant increase through the course of treatment.
5. ALP: statistically insignificant increases at 3m, and insignificant decreases thereafter.
6. TSH: There is statistically significant increases at 6m and 18m.
7. HB: there is statistically significant decreases in all stages when compared to basal level and statistically significant increases from 20w till 44wwhen compared to 2w,4w,12w.
8. Platelets: there is statistically significant decreases till 28w, thereafter there is insignificant increases at 36,44w.
9. WBC_s: there is significant decreases at 12w,20w,28w,36w when compared to the basal levels. As regard the non responder group:

    1- PCR: PCR levels are still detectable at 3m and did not decrease by 2 logs at least.
    2- ALT, AST: insignificant increase at 3m
    3- T. bilirubin: insignificant increase at 3m
    4- D. bilirubin: insignificant decrease at 3m
    5- ALP: insignificant increase at 3m
    6- TSH: insignificant decrease at 3m
    7- HB: significant decreases at 2w,4w,12w when compared to basal levels.

8- Platelets: insignificant decrease at 2w,4w,12w when compared to basal levels.
9- WBC_S: insignificant decrease at 4w,12w when compared to basal level

As regard the break through group:

1) PCR: there is a detectable (+ve) PCR levels at the time of detection of the break through (6m or 9m).
2) ALT, AST: there is statistically insignificant increases at 3m, also at 6m or 9m(time of break through detection)
3) Bilirubin T: Insignificant increases at 3m,6m when compared to basal levels.
4) Bilirubin D: Insignificant increases at 6m
5) ALP: Insignificant increases at 3m,6m when compared to basal levels.
6) TSH: Insignificant increases at 3m,6m when compared to basal levels.
7) HB: significant decreases at 4w,12w when compared to basal levels.
8) Platelets count: insignificant decreases at 2m, 4m,12w,20w when compared to basal levels.
9) WBC count: significant decreases at 4w,12w,20w, when compared to basal levels.

As regard the CBC changes of the overall cases of the study:

- The hemoglobin level had decreased to less than 10 g/dl in 69% of the cases and decreased less than 8 g/dl in 4% of the cases.
- The platelet count had decreased to less than $80x10^9$/L in 10% of cases and decreased to less than $50x10^9$/L in 2% of cases, and to less than $25x10^9$/L in 1% of cases.
- The WBC_s count had decreased to less than $4x10^9$/L in 40% of cases and decreased to less than $2x10^9$/L in 3% of cases.

As regard the side effects of such therapy that were reported by our patients during the course of the treatment, our study revealed that:

- 100 % of the cases reported flu like symptoms for a few days after interferon injection.
- 93% of cases reported fatigue as a mean complaint during therapy.
- 45% of cases reported skin rash.
- 21% of cases reported headache as a disturbing symptom during treatment.
- 18% of the cases reported vomiting
- 15% of the cases reported nausea
- 13% reported joints pains (arthralgia) especially after interferon injection
- 4% reported weight loss which is noted after completion of therapy (48w).
- 4% the cases reported tinnitus that was usually mild
- 2% of the cases reported anorexia

- And one case reported symptomatic hypothyroidism with a TSH level elevation to 11.2 mu/l at 12m.
- Also one case reported bronchitis with spasm (asthma like symptoms). also one case reported mild depressive symptoms, and one case of recurrent syncopal attacks during treatment.

When comparing side effects of peg interferon/ Ribavirin combination therapy in our study to (Kamal et al, 2005) study, Kamal et al study revealed the following:

- In the group that achieved S.V.R side effects was as follow:

66%	fatigue	19% pruritus	6% dizziness
63%	Influenza like	19%anorexia	5%vomiting
62%	headache	18%arthralgia	
62%	myalgia	16%dyspnea	
62%	pyrexia	13%rash	
49%	insomnia	9%diarrhea	
42%	Injection site erythema	9%depression	
32%	irritability	9%dry mouth	
31%	Back pain	7%abdominal pain	
42%	Rigors	7%alopecia	
21%	sore throat	7%nausea	
21%	cough	7%dry skin	

As regard cases that had stopped treatment prematurely in our study we classified them into two groups:

❖ The first group are those who stopped treatment due to side effects or complications of therapy and they were as follows:

☒ One case stopped treatment at 30 w due to hemiplegia that started as gradual hemiparesis.

☒ Also one case stopped treatment at 14 w due to severe visual field disturbance, also one case that experienced recurrent effort related chest pain and dyspnea and diagnosed as ischemic heart disease at 13 w.

☒ Also one case stopped treatment due to severe aneamia (HB<6g/d1) not tolerated by the patient and persistant inspite blood transfusion and epo therapy at 20 w.

☒ Two cases stopped treatment at 24w due to severe incapacitating fatigue, and one female 32 years old case stopped treatment at 12w because she became pregnant despite an (IUD) contraception.

☒ The second group of patients that had stopped treatment are those who were non responders 7% and those who experienced a break through (4%)(of all the study cases).

☒ So the overall cases that had stopped treatment were 18 patients (18%), of these:

- 7 patients (7%) non responders
- 4 patients (4%) break through
- 7 patients (7%) due to side effects or complication of therapy

SUMMARY AND CONCLUSION

Egypt has the highest HCV antibody prevalence in the world nearly14.7% of Egyptian population. The start of the epidemic is attributed to insufficiently sterilised intravenous injections during the mass anti-schistosomiasis treatment campaigns in rural areas during the 1970s. Spread of HCV has therefore been studied mainly in rural areas. An early survey documented HCV clustering among households of individuals with history of parenteral treatment for schistosomiasis. More recently, in cohort studies of rural areas of Egypt, having an anti-HCV-positive family member was the strongest predictor for incident HCV infection, after adjustment for iatrogenic and community exposures. Also, a mathematical model estimated that within HCV-infected couples, 6% would have acquired their infection from their partners.

Treatment of chronic HCV genotype 4 infection in Egypt was depending on acombination of peg interferon and ribavirin but recently a directly acting anti viral drug sofosbuvir will be add to this regimen to improve treatment out comes

From this point we designed our study to study the response of our Egyptian patients with chronic HCV geno type

4 infection to the combination therapy of Interferon/Ribavirin and to study the side effects of such regimen and to determine cases that had stopped treatment prmaturly and why.

We randomly selected 100 patients who were already candidate for inf/rib therapy from the outpatient Hepatology Clinic in Al Mebara Hospital at Kafer Eldawar city at Al Behira Governorate who had completed their course of treatment and followed them retrospectively by history taking ,clinical examination and laboratory investigation where followed at (0-3-6-12-18) months of treatment by PCR for HCV-ALT-AST-ALP-TSH-S.billrubin (total-direct) and C.B.C at (0-2-4-12-20-28-36-44) weeks of treatment .

Data were collected, tabulated and statistically analysed and revealed the following:

- Our study revealed that 71% of the cases had achieved S.V.R, 11% relapses, 7% non responders, 4% of break thought.
- Our study also revealed that 7% of the cases had stopped treatment due to side effects or complication of therapy.
- Our study revealed also that the common side effects encountered during therapy are: flu like symptoms, fatigue, rash; headache, vomiting , nausea, arthralgia, dizziness.

- Cases that had stopped treatment due to side effects or complications of therapy where 7% where due to neurological causes as hemiplegia and sensory affection as visual field disturbance. Cardiovascular causes as ischemic heart disease, haematological affection as severe anemia also sever incapacitating fatigue.

From our study we concluded that inf/rib regemin in Egyptian HCV genotype 4 patients needs along duration of therapy (12 months) to achieve S.V.R that never reached 75% in all studies, with a long list of distressing side effects and serious neurological, C.V.S, endocrine and haematological effects, that always affect the patient compliance and response to treatment which eventually adversely affect the cure rates of HCV in Egypt.

It's recommend the use of the new direct acting antiviral drug sofosbuvir where studies recorded a S.V.R rates of nearly 96% in a 3 months duration of therapy for HCV genotype 4 patients and to study the response of Egyptian HCV +4 patients to its regimen and their compliance to this treatment.

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الملخص العربى

مصر لديها أعلى معدلات انتشار الأجسام المضادة لفيروس الالتهاب الكبدى الوبائى سى (HCV)في العالم ما يقرب من 14.7 ٪ من سكان مصر . ويعزى بداية هذا الوباء فى مصر لعدم التعقيم بشكل جيد للحقن المستخدمة فى العلاج خلال حملات العلاج المضاد لمرض البلهارسيا في المناطق الريفية خلال 1970 .ولذلك فقد تم دراسة انتشار فيروس التهاب الكبد الوبائى سى (HCV) بشكل رئيسي في المناطق الريفية .توثيق استطلاع في وقت مبكر اوضح ان فيروس التهاب الكبد الوبائى سى (HCV) تجمع بين افراد الأسر التى لديها تاريخ من العلاج بالحقن لمرض البلهارسيا . وفي الآونة الأخيرة، في دراسات الأتراب من المناطق الريفية في مصر، فانه اذا كان احد افراد العائلة لدية الاجسام المضادة لفيروس التهاب الكبد الوبائى سى (HCV AB) فان ذالك مؤشر قوى لامكانية احتمال الاصابة بـفيروس التهاب الكبد الوبائى سى (HCV) فى اى من أفراد العائلة و أيضا اوضح نموذج رياضي أنه بين الأزواج المصابين بفيروس التهاب الكبد الوبائى سى (HCV) فان ٪ 6 منهم قد اكتسب العدوى من شركائه .

ان علاج الاصابة المزمنة بفيروس التهاب الكبد الوبائى سى(HCV) من النوع الجينى الرابع فى مصر كانت تعتمد على علاج مركب من عقارى الانترفيرون و الريبافيرين و لكن فى الاونه الاخير تم اضافة عقار السوفوسبوفير الى هذا العلاج و ذلك لتحسين نتائج العلاج .

و من هذا المنطلق فقد قمنا بعمل هذة الدراسة لدراسة استجابة المرضى المصريين المصابين بعدوى مزمنة بفيروس التهاب الكبد الوبائى سى(HCV) من النوع الجينى الرابع للعلاج المركب من عقارى الانترفيرون و الريبافيرين و

توضيح الاثار الجانبية لهذا العلاج و توضيح الحالات التى لم تكمل علاجها و الاسباب المحتملة لذالك .

و فى هذة الدراسة فقد قمنا باختيار 100 حالة مصابة بعدوى مزمنة بفيروس التهاب الكبد الوبائى سى (HCV) من النوع الجينى الرابع من العيادة الخارجية لامراض الكبد من مستشفى المبرة للتأمين الصحى بمركز كفر الدوار بمحافظة البحيرة و الذين اكملوا العلاج بالانترفيرون و الريبافيرين و تم متابعتهم باثر رجعى بمعرفة التاريخ المرضى لهم و فحص طبى كامل و بعض الفحوصات المعملية فى الفترات التالية من العلاج :- عند بداية العلاج و بعد 3 اشهر و بعد 6 اشهر و 12 شهر و بعد 18 شهر من العلاج وشملت الفحوصات المعملية الاتى :- التحليل الكمى لى فيروس سى HCV PCR و انزيمات الكبد ALT.AST و الانزيم المنشط للغدة الدرقيةTSH و انزيم الفوسفاتيز القلوىALP و الصفراء بالدم (كلى و مباشر) S.BILLIRUBINو ايضا صورة دم كاملة C.B.Cفى بداية العلاج و بعد أسبوعين و بعد 4 اسابيع ثم مرة كل 8 اسابيع حتى نهاية العلاج.

و تم تجميع البيانات الناتجة ، وجدولتها وتحليلها إحصائيا وكشف ما يلي:

1- 71 % من الحالات قد حققت استجابة فيروسية مستدامة و 11 % حدث اعادة ظهور للفيروس بعد انتهاء فترة العلاج و 7 % غير مستجيبين للعلاج و 4 % اعادة ظهور للفيروس خلال فترة العلاج

2- 7 % من الحالات اوقفت العلاج خلال فترة العلاج و ذلك بسبب الاعراض الجانبية للعلاج

3- لقد كانت الاعراض الجانبية الاكثر شيوعا خلال فترة العلاج هى اعراض شبية بالانفلونزا و ارهاق و صداع و طفح جلدى و قئ او ميل للقئ و الم بالمفاصل و دوخة

4- و الحالات التى اوقفت العلاج بسبب الاعراض الجانبية كانت بسبب ظهور اعراض عصبية مثل شلل نصفى و اعراض حسية مثل ضعف فى الابصار و اعراض تاثر القلب مثل اعراض قصور الشريان التاجى و الانيمياء الشديدة الغير مستجيبة للعلاج و الارهاق الشديد الغير محتمل.

و من دراستنا استنتاجنا ان علاج العدوى المزمنة ب فيروس التهاب الكبد الوبائى سى (HCV) من النوع الجينى الرابع فى مصر بعقارى الانترفيرون و الريبافيرين يحتاج الى فترة زمنية طويلة (12 شهر) لتحقيق استجابة فيروسية مستدامة و التى لم تبلغ 75 % ابدا فى الدراسات السابقة و كذلك فى دراستنا و ايضا ينتج عن هذا العلاج الكثير من الاعراض الجانبية و له مضاعافات خطيرة على الجهاز العصبى و القلب و الغدد الصماء و الدم و التى تؤثر بالسلب على استكمال المريض لفترة العلاج و بالتالى تؤثر بالسلب على معدلات الشفاء من العدوى .

و لذلك فانه ينصح بالتوسع فى استخدام عقار السوفوسبوفير لعلاج العدوى المزمنة بفيروس التهاب الكبد الوبائى سى (HCV) من النوع الجينى الرابع فى مصرحيث قدرت الدراسات ان نسبة تحقيق الاستجابة الفيروسية المستدامة عند استخدام هذا العقار قد تصل الى 96 % فى فترة علاج 3 اشهر فقط و ايضا ننصح بدراسة استجابة المرضى المصريين لهذا العقار و الاعراض الجانية التى قد تظهر من هذا العلاج بعد التوسع فى استخدامة

الاستجابة الفيروسية المستدامة فى المرضى الذين يعانون من عدوى مزمنه بفيروس الالتهاب الكبدى الوبائى c من النوع الجينى 4 الذين يعالجون بعلاج مركب من عقارى الانترفيرون والريبافيرين.

رسالة مقدمه من الطبيب

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بكالوريوس الطب والجراحه

توطئة للحصول على درجة الماجستير فى امراض الباطنه

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