

## RECOMMENDATIONS

Several recommendations could be extracted based on the results of the present study:

- Further studies should be carried out considering larger sample size, measurement of IL-28 B itself, pharmacogenomics and other genetic polymorphism of IL-28B or other genes involved influencing response to treatment. Also, virus genotype and subtypes should be investigated.
- Age, GGT, lipid profile, BMI, and IL-28B polymorphisms are the strongest pretreatment predictors of response to pegylated interferon and ribavirin, therefore, they should be considered in treating patients with chronic HCV genotype 4.
- In liver transplantation IL28B polymorphism in the donor and recipient should be considered.
- The very high prevalence of insulin resistance and its known association with poor treatment outcomes may recommend its consideration before starting the treatment.
- Treatment with a single-tablet regimen containing ledipasvir and sofosbuvir resulted in high rates of sustained virologic response among patients with HCV genotype 1 infection who had not had a response to prior interferon-based treatment. The patients had a non-CC IL28B genotype. Ledipasvir (Gilead Sciences) is a new HCV NS5A inhibitor with potent antiviral activity against HCV genotypes 1a and 1b. Sofosbuvir is a nucleotide polymerase inhibitor approved for the treatment of HCV genotypes 1 through 4 in combination with ribavirin, with or without peginterferon.
- In the near future, several issues could be addressed. The seromarkers, serum HCV RNA and ALT levels could be used to predict subsequent risk of HCV related hepatocellular carcinoma, indicating that the seromarkers have potential to be used as pretreatment markers in clinical decisions to classify high-risk patient who need intensive care.

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## المخلص العربي

تعد مصر واحدة من أكثر دول العالم التي ينتشر بها مرض التهاب الكبد الوبائي فيروس سي انتشاراً واسعاً وقد وجد أن النوع الجيني الرابع هو الأكثر انتشاراً في مصر.

ومن جهة أخرى، فقد وجد أن نسبة نجاح علاج فيروس التهاب الكبد الوبائي عن طريق الإنترفيرون مع الريبافيرين تصل إلى ٥٠٪ وعلي هذا فإنه من الضروري دراسة وفهم أسباب عدم الاستجابة للعلاج وذلك للتغلب عليها وكذلك التعرف على العوامل التي يمكن أن تنبئ بمدى استجابة كل مريض للعلاج. هناك عوامل متعددة تؤثر على الاستجابة للعلاج وتشمل: (١) العوامل المتعلقة بالفيروس، (٢) العوامل المتعلقة بالمريض.

وعلي هذا فإن الهدف من هذا البحث هو ألقاء المزيد من الضوء على تأثير بعض العوامل الخاصة بالفيروس والمريض على الاستجابة للعلاج بالإنترفيرون مع الريبافيرين في حالات مرضي التهاب الكبد الوبائي (فيروس سي).

وقد تم إجراء هذه الدراسة على ثلاثين فرداً من الأصحاء وثمانين وثمانين حالة من مرضي التهاب الكبد الوبائي (فيروس سي). وقد تم إجراء الفحوصات الإكلينيكية والمعملية مثل وظائف الكلى والكبد وصورة الدم الكاملة واختبارات خاصة بوجود فيروسات التهاب الكبد وكميته في الدم كما تم قياس مستوى الدهون بأنواعها وكذلك مستوى مقاومة الأنسولين.

وقد أظهرت نتائج البحث أن هناك خلل واضح في وظائف الكبد للمرضى حيث وجد ارتفاع في أنزيمات الأمينوترانسفيراز والفسفاتيز القاعدي والجاما جلوتاميل ترانسفيراز والصفراء والألبومين مما يدل على تدمير خلايا الكبد نتيجة الإصابة بالفيروس.

كما تم دراسة تأثير التنوع الجيني للأنترليوكين ٢٨ بي على مدى الاستجابة لعلاج الإصابة بفيروس التهاب الكبد الوبائي سي المزمن. كما أظهرت النتائج وجود ارتفاع كبير في مستوى الدهون ثلاثية الجليسرول مع انخفاض كبير في مستوى الكوليسترول الكلي ومعدل الليبوبروتين الأقل كثافة. ولهذا تلقى الضوء على دور الدهون في دخول فيروس التهاب الكبد الوبائي (سي) إلى خلايا الكبد وتكاثره.

وفي الوقت ذاته فقد أظهرت النتائج أن هناك ارتفاع في مستوى السكر الصائم ومستوى الأنسولين في مرضي التهاب الكبد الوبائي (فيروس سي). وقد ورد أن المستويات العالية من الأنسولين والجلوكوز في الدم قد تؤدي إلى تكوّن الألياف عن طريق استمرار حث إطلاق عامل نمو النسيج الليفي من خلايا الكبد المتليفة بالدهون.

ومن الجدير بالذكر، إن النتائج أظهرت أن ٦٤٪ من المرضى استجابوا إلى العلاج بينما لم يستجب ٣٦٪ من المرضى للعلاج. كما ذكر من قبل فإن العوامل المؤثرة على الاستجابة للعلاج تنقسم إلى: عوامل خاصة بالفيروس وعوامل خاصة بالمريض ومن العوامل الخاصة بالفيروس هو كم الفيروس. وبالرغم من نقص الدلالة الإحصائية فقد أظهرت النتائج أن كمية الفيروس سي في المرضى المستجيبين أعلى من كميته في المرضى الغير مستجيبين للعلاج. وتشير النتائج إلى وجود عوامل أخرى خاصة بالمريض والعوامل الفيروسية في توقع استجابة الفيروس كلياً للعلاج. كما لم تظهر أختلافاً مؤثراً بين متوسط عمر المستجيبين للعلاج عن متوسط عمر غير المستجيبين للعلاج.

وفي نفس الوقت، فقد وجد عن أن أنزيم الجاما جلوتامات يعد من العوامل المستقلة التي تنبئ بمدى الاستجابة للعلاج فعندما يكون مستوى نشاطه منخفض في دم المرضى يكون لديهم فرصة أكبر في الاستجابة للعلاج بنسبة ٨٨٪.

ولقد أوضحت الدراسة الحالية أيضاً أن المرضى الذين يعانون من السمنة المفرطة بالأعتماد على نتائج فهرس كتلة الجسم تقل لديهم فرص الاستجابة للعلاج بنسبة ٨٥٪ مقارنة بالمرضى ذوي كتلة الجسم الطبيعية.

وعلاوة على ذلك، فقد تم التوصل إلى وجود علاقة بين مقاومة الأنسولين والاستجابة الضعيفة للعلاج المضاد لفيروس سي. فقد توصلت الدراسات السابقة أن مقاومة الأنسولين بالقيمة المرجعية (٢) تعد عاملاً سلبياً له دور في التأثير على الاستجابة التامة للعلاج. وأظهرت نتائج الدراسة الحالية عن وجود نقص بنسبة ٢١.٥٪ في معدل الاستجابة للعلاج إذا ما زادت عن هذه القيمة المرجعية.

كما أظهرت الدراسة أن وجود تجمع دهني في الكبد و وجود تليف ملحوظ بمعدلات عالية و كبيرة في مرضى الألتهاب الكبد الوبائي (فيروس سي) المزمّن هو أيضا من العوامل التي تعوق فرصة الاستجابة التامة للعلاج. فقد أوضحت النتائج أن المراحل المتقدمة من التليف تقلل فرصة استجابة الفيروس للعلاج بمعدل ١٧%.

ومن العوامل الخاصة بالمرضى والمرتبطة باستجابته لعلاج التهاب الكبد الوبائي (فيروس سي) هو التعدد الجيني للأنترليوكين بي ٢٨ فقد ورد أن المرضى حاملى الطراز الجيني CC (rs12979860) للأنترليوكين بي ٢٨ من العوامل التي تتنبئ بمدى استجابة المريض للعلاج. وكشفت بيانات الدراسة الحالية أن النوع الجيني CC (rs12979860) للأنترليوكين بي ٢٨ للمرضى يكون معدل الاستجابة للعلاج في هذا النوع (٩١.٣%) أعلى من نسبة المرضى غير المستجيبين للعلاج (٨.٧%) للحاملين لهذا النوع الجيني. وكشفت النتائج أحصائيا أيضا عن وجود ارتباط وثيق بين النوع الجيني CC والاستجابة للعلاج بالانترفيرون مع الريبافيرين فمعدلات الاستجابة معتمدة على التنوع الجيني هذا ل(rs12979860) كانت النسب التقريبية لها هي ٩١%، ٥٧% و ٥٠% لأنواعه المتعددة الجينية وهي CC و CT و TT على التوالي.

وعلى الجانب الآخر، فقد تم دراسة تأثير النوع الجيني CC للأنترليوكين بي ٢٨ rs12979860 على عملية أيض الدهون. وقد أظهرت دراسات متعددة ما يتفق مع الدراسة الحالية أن المرضى ذو النوع الجيني CC للأنترليوكين بي ٢٨ كان لديهم ارتفاع في الكوليسترول الكلى والدهون الأقل كثافة. وتؤكد نتائج الدراسة الحالية الاقتراح بأن الترابط الملحوظ والمرتبطة بشكل مباشر بتفاعل المرضى و فيروس سي بدلا من التأثير المباشر لهذا النوع الجيني وهذه النقطة على عملية أيض الدهون. وكان هذا الاقتراح معتمدا على ملاحظة النوع الجيني CC للأنترليوكين بي ٢٨ كان يتم رؤيته غالبًا في النوع الجيني الثالث للفيروس والمرضى غير المصابين بالعدوى أكثر منه في النوع الجيني الأول والرابع للفيروس.

ومن الملفت للانتباه في نتائج الدراسة الحالية تكرار ظهور ارتفاع درجة معدلات التليف والأنزيمات الحاملة للجاما جلوتومات في مرضى التهاب الكبد الوبائي (فيروس سي) الغير مستجيبين للعلاج والذين ليس لديهم هذا النوع الجيني CC من الأنترليوكين بي ٢٨. وقد تم ملاحظة وجوده مع الأنواع الجينية الأخرى الخاصة بالعائل TT و CT للأنترليوكين بي ٢٨ (rs12979860) مع ملاحظات عدة لعدة الكبد وتلفه خلاياه وحدة مرضه.

وفي الختام، تعد الدراسة الحالية محاولة لإلقاء المزيد من الضوء على تأثير العوامل المتعددة الخاصة بالمرضى والعوامل الخاصة بالفيروس على مدى الاستجابة للعلاج الأساسي للعناية بمرضى الألتهاب الكبد الوبائي. وقد كشفت نتائج الدراسة الحالية عن أن أنزيمات الجاما جلوتومات ودلالات معدل كتلة الجسم ومقاومة الانسلولين وتليف الكبد تعطى توقعا هاما و ضروريا كل منها مستقلا لاستجابة الفيروس للعلاج والقضاء عليه.

تأثير التعدد الجيني لجين الأنترلوكين بي ٢٨ وبعض العوامل الخاصة بالعائل علي  
أستجابة المصريين لعلاج الأنترفيرون/ ريبافيرين في مرضي الالتهاب الكبدي سي

رسالة

مقدمة إلى معهد البحوث الطبية- جامعة الإسكندرية  
ايفاءا جزئيا لشروط الحصول على درجة

الماجستير

في

الكيمياء الطبيه التطبيقية

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معهد البحوث الطبية

جامعة الإسكندرية

٢٠١٤

تأثير التعدد الجيني لجين الأنترلوكين بي ٢٨ وبعض العوامل الخاصة بالعائل علي أستجابة  
المصريين لعلاج الأنترفيرون/ ريبافيرين في مرضي الالتهاب الكبدي سي

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للحصول على درجة

الماجستير

في

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