Case Report

Combination effect of ribavirin and erythropoietin treatment on hemoglobin A1c in a diabetic patient with chronic hepatitis C

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Abstract

Any condition that shortens erythrocyte lifespan or decreases mean erythrocyte age may falsely lower hemoglobin A1c (A1C) test results. Ribavirin (RBV) used for chronic hepatitis C virus (HCV) infection can cause reversible hemolytic anemia; erythropoietin (EPO) used for treatment-related anemia can stimulate the production of red blood cells. We reported a 55-year-old woman with diabetes who received peginterferon alfa plus RBV for HCV infection. Four weeks following HCV therapy, her Hb level declined from 13.3 g/dL to 11.3 g/dL with elevated lactate dehydrogenase and reduced haptoglobin, which confirmed hemolysis. As her Hb fell to a nadir of 8.5 g/dL at the eighth week, darbepoetin alfa was administered to treat anemia consecutively for 10 weeks. Two months later, the patient’s A1C declined from 7.5% to an extremely low value of 4.0%, accompanied by a fasting glucose level of 116 mg/dL. During the preceding 3 months, there was no self-reported hypoglycemia or documented low blood glucose. About 3 months after HCV therapy was terminated, the A1C returned to 6.1% without medication adjustment. The concurrent use of RBV and EPO treatments can synergistically cause falsely low A1C values and may lead to inappropriate relaxation of glycemic control. During HCV treatment with RBV, A1C should not be used alone to guide diabetes therapy.

Keywords: chronic hepatitis C; diabetes; erythropoietin; HbA1C; ribavirin

1. Introduction

Hemoglobin A1c (A1C) has been widely used to estimate glycemic control in diabetic patients. Recently, A1C has been further recommended as a preferred diagnostic test for diabetes.1 However, there are clearly limitations in the measurement of A1C. Any condition that shortens erythrocyte survival or decreases mean erythrocyte age may falsely lower A1C test results regardless of the assay method used.2

There is growing evidence suggesting the mutual link between type 2 diabetes mellitus (DM) and chronic hepatitis C virus (HCV) infection. Based on case-control studies, the prevalence of DM had been reported in 21% to 24% of patients with HCV infection, which was significantly higher than that in the general population.3,4 Although clinicians realized that there is some relationship between HCV and DM, most were unaware of the impact of HCV therapy on A1C test results. Combination therapy with ribavirin (RBV) and peginterferon alfa (peg-IFN) is the current standard care for patients with HCV infection. RBV has been shown to induce reversible hemolytic anemia with shortened erythrocyte survival.5,6 This anemia would be more pronounced with a combination of IFN and RBV because the myelosuppressive effect of IFN inhibits the bone marrow to compensate for RBV-induced hemolysis.7 In addition, erythropoietin (EPO), commonly used for anemia related to HCV therapy, can stimulate production of red blood cells with decreased mean erythrocyte age.8 Herein, we reported a diabetic woman who received RBV plus peg-IFN for HCV and then darbepoetin alfa for subsequent anemia. The concurrent use of RBV and EPO caused an unexpectedly low A1C value.

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2. Case report

A 55-year-old woman with type 2 diabetes for 3 years visited our diabetes clinic for glucose control. She had been taking metformin 1000 mg daily. Laboratory study showed an alanine transaminase (ALT) level of 203 U/L and an aspartate aminotransferase (AST) level of 170 U/L. Screening of hepatitis marker revealed the patient was positive for hepatitis C antibody. Hence, she was referred to a hepatologist for further treatment. A subsequent liver biopsy confirmed mild chronic hepatitis C with periporal fibrosis, and further analysis proved she was a HCV genotype 1b infected patient. She started HCV therapy with peg-IFN alfa-2b 80 mcg weekly and RBV 800 mg daily.

Before HCV therapy, the patient’s fasting plasma glucose level was 120 mg/dL and her simultaneous A1C value was 6.8% (Table 1). One month after treatment, the fasting glucose level elevated to 137 mg/dL with A1C value rising to 7.5%. Thus, sitagliptin was added to her drug regimen for better glycemic control. At the same time, her Hb declined to 11.3 g/dL, accompanied by a lactate dehydrogenase (LDH) level of 215 U/L, and a haptoglobin value of less than 10 mg/dL. Liver function test showed both ALT and AST levels were within normal limits. However, after 2 months treatment, Hb continued to decline to 8.3 g/dL. In addition to a reduction of RBV dose, the hepatologist prescribed darbepoetin alfa 20 mcg weekly for treatment of anemia. Four months following her HCV therapy, the A1C value fell to an unexpectedly low value of 4.0%, with simultaneously measured fasting glucose level of 116 mg/dL. During the preceding 3 months, there was no self-reported hypoglycemia or documented low blood glucose. Three months later, the measured A1C still showed a very low value of 4.1% accompanied by fasting glucose level of 110 mg/dL. Since hemolysis-related falsely low A1C was highly suspected, we did not change the dosage of oral antidiabetic drugs.

Following 3 months after the end of HCV therapy, the A1C value, as well as Hb level, returned to near their baseline levels without further medication adjustment. It was noteworthy that RBV was used throughout the entire course of treatment, with a reduced dose only when Hb levels declined to less than 10 g/dL, and where EPO was used to treat anemia continuously for 10 weeks.

3. Discussion

Although the international standardization of the A1C assay has decreased potential technical errors in interpreting A1C results, there are other biologic and patient-specific factors that may cause misleading results. Depending on the methodology, genetic variants and chemically modified derivatives of Hb can affect the accuracy of A1C measurements. Moreover, higher A1C values in relation to mean glucose levels can be obtained when red blood cell turnover is low. For example, patients with iron, vitamin B12, or folate deficiency anemia can generate falsely high A1C values. By contrast, any condition that increases erythrocyte turnover, such as recovery from acute blood loss or hemolytic anemia, will falsely lower A1C values because of the shorter exposure of Hb to circulating glucose.

A study by Panzer et al. found a strong linear correlation between A1C values and red blood cell survival ($r^2 = 0.88, p < 0.001$) in non-diabetic patients with autoimmune-induced hemolytic anemia. They established the usefulness of A1C as a screening test for hemolysis in patients without diabetes. Thereafter, discordant results between low A1C and high blood glucose levels have been reported in diabetic patients with hemolysis of various etiologies, such as malaria, hereditary spherocytosis, and drug-induced hemolysis (dapsone and trimethoprim/sulfamethoxazole).

Oral RBV plus peg-IFN is the current standard therapy for chronic HCV infection. The primary toxicity associated with
the use of RBV is hemolytic anemia. RBV, a synthetic oral nucleoside analogue, is concentrated within erythrocytes and results in a relative deficiency of adenosine triphosphate (ATP), and, hence, increases patient susceptibility to oxidative damage and extravascular hemolysis.\(^5\) RBV is the major contributor to treatment-associated anemia. During HCV therapy, our case demonstrated Hb declined from 13.3 g/dL at baseline to the nadir of 8.3 g/dL at the eighth week of treatment. The combination of an increased serum LDH and a reduced haptoglobin confirmed the occurrence of hemolysis. The initial missing reticulocyte response may be due to the myelosuppressive effect of IFN. However, after continuing RBV therapy with the use of EPO for anemia, the subsequent reticulocyte percentage increased to more than 10% at the twelfth week of treatment.

Our case showed the A1C value increased from 6.8% at baseline to 7.5% at the fourth week of treatment with a parallel change in fasting glucose level of 120 mg/dL to 137 mg/dL. The etiologies of initial hyperglycemia might be multifactorial, including the stress from treatment-related unpleasant side effects, such as flu-like symptoms.\(^13\) Sitagliptin, an oral dipeptidyl peptidase-4 (DPP-4) inhibitor, was then added to achieve better glycemic control. Based on previous clinical trial, sitagliptin, when added to ongoing metformin therapy, has been shown to reduce mean A1C by 0.65% (−0.77 to −0.53), and fasting plasma glucose by 25.4 mg/dL (−31.0 to −19.8).\(^14\) However, our case demonstrated a fall in fasting glucose by 21–27 mg/dL accompanied by a decline in A1C by 3.4%–3.5%; a large discrepancy of more than 2.5% between measured and estimated A1C values was observed. In addition, there was no self-reported hypoglycemia or documented low blood glucose level in this case. The unexpectedly low A1C values of either 4.0% or 4.1%, below the usually quoted reference range for non-diabetic people, were clearly inaccurate measures. It was our first impression that concurrent anemia of a hemolytic nature could be the major contributor to the false A1C decline.

To our knowledge, three cases have been reported to highlight the impact of RBV-induced hemolysis on A1C measurement in diabetic patients.\(^12,13,16\) Following treatment with IFN/RBV, the falsely low A1C values of 4.1% to 4.9% were observed in these patients (Table 2). However, the low A1C value of 4.7% in the diabetic patient reported by Tahrami et al.\(^17\) might have been misinterpreted. The authors did not address any relationship between RBV therapy and A1C measurement; they even stated diabetes had been resolved during IFN/RBV therapy.

Few investigators have examined the effect of IFN/RBV on A1C. Greenberg et al.\(^18\) conducted a retrospective analysis on 32 diabetic participants receiving IFN plus RBV therapy. Their study revealed a significant decline in A1C values of 2.0%, but matched random glucose levels also decreased significantly by a mean of 38.4 mg/dL after HCV therapy. Using the equation derived from the Diabetes Control and Complications Trial to estimate the contribution of glucose change to the decline in A1C value, they concluded that RBV-induced hemolysis contributed to the A1C change by only 0.93%. Therefore, according to this study result, the large decline in A1C value relative to glycemic change in our case led us to consider other interfering factor on the measurement of A1C.

In addition to RBV-induced hemolysis, consecutive EPO therapy for 10 weeks in our case might play a role in the determination of A1C value. EPO, a glycoprotein growth factor widely used in the management of anemia due to chronic kidney disease (CKD), is the primary stimulus to erythropoiesis, promoting the terminal differentiation of erythroid colony-forming units (CFU-E) into normoblast and then erythrocyte. EPO has not been approved by the U.S. Food and Drug Administration for treatment of anemia in patients undergoing treatment for HCV. Nevertheless, it is used commonly under such circumstance in clinical practice. Since EPO therapy can stimulate the production of red blood cells, as indicated by reticulocytosis in our case, it may also cause falsely low A1C values. Several studies have demonstrated a fall in A1C values following EPO therapy in patients with diabetes and CKD.\(^19,20\) A well-designed prospective study conducted by Ng et al.\(^20\) revealed a mean reduction in A1C value of 0.7%, without a change to glycemic control following EPO therapy. Another study in non-diabetic patients with CKD reported a mean decline in A1C value of 1.2% following EPO and iron therapy.\(^21\) The combination of EPO and iron might contribute to the large and artificial decline in A1C value compared to the result by Ng et al. Therefore, the use of EPO, which could enhance the A1C-lowering effect triggered by RBV-induced hemolysis, might be a plausible explanation.

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Table 2
Profiles of A1C, fructosamine and blood glucose levels in reported diabetic patients receiving interferon and ribavirin for hepatitis C.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Pre-Rx A1C (%)</th>
<th>Pre-Rx BG (mg/dL)</th>
<th>On-Rx A1C (%)</th>
<th>On-Rx fructosamine (µmol/L)</th>
<th>On-Rx BG (mg/dL)</th>
<th>Post-Rx A1C (%)</th>
<th>Post-Rx BG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Polgreen</td>
<td>50</td>
<td>M</td>
<td>NA</td>
<td>NA</td>
<td>N</td>
<td>High</td>
<td>155</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2006</td>
<td>Tahrami</td>
<td>40</td>
<td>M</td>
<td>7.7</td>
<td>NA</td>
<td>4.7</td>
<td>NA</td>
<td>112</td>
<td>8.2 (6 m)</td>
<td>NA</td>
</tr>
<tr>
<td>2008</td>
<td>Robertson</td>
<td>55</td>
<td>M</td>
<td>NA</td>
<td>4.4</td>
<td>4.9</td>
<td>317*</td>
<td>72–162</td>
<td>6.5 (3 m)</td>
<td>72–126</td>
</tr>
<tr>
<td>2009</td>
<td>Gross</td>
<td>59</td>
<td>M</td>
<td>7.3</td>
<td>4.1</td>
<td>4.8</td>
<td>NA</td>
<td>72–126</td>
<td>6.5 (1 m)</td>
<td>72–126</td>
</tr>
</tbody>
</table>

A1C = hemoglobin A1c; BG = blood glucose; F = fasting; M = male; m = months; N = normal; NA = not available; PC = postprandial; Rx = treatment.

* Normal range : 202-285 µmol/L.
for the very low A1C value in our case. To our knowledge, the effect of concurrent use of EPO and RBV on A1C has never been addressed in the same patient.

The importance of routinely assessing A1C in diabetic patients is well established. Institutional performance in the diabetes arena may be judged by the proportion of patients is well established. Institutional performance in the diabetes arena may be judged by the proportion of patients treated for diabetes inadequately controlled with metformin therapy. At the present time, frequent self-monitoring of blood glucose remains the best alternative to obtain the most accurate assessment of glycemic control in this patient group.

References


