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LETTER TO EDITOR

Pegylated Alpha Interferons: An Unresolved Clash of the Titans?

Andres Duarte-Rojo, Jordan Jay Feld, Elizabeth Jenny Heathcote *

Liver Centre, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada

Dear Editor,

Physicians treating chronic hepatitis C (CHC) have witnessed a fascinating evolution of therapies, from the initial experimental alpha interferon (IFN- α) in non-A/non-B hepatitis, to the new STAT-C era of specific targeted antivirals. Over these past 25 years, two events stand out as major breakthroughs in therapy for CHC: the addition of the antiviral agent ribavirin (RBV), which allowed doubling of the sustained virologic response (SVR) from ~20 to ~40%; and the alpha peginterferon (PEG-IFN-α) which further improved the rate of SVR to 55% by lengthening the half-life of IFN-α [1]. Nonetheless, IFN-α (whether pegylated or not) remains until today a constant in the armamentarium against CHC, and it may not disappear even in the STAT-C era.

Post hoc analysis of the registration trial for PEG-IFN-α2b showed that higher doses of RBV were associated with a higher rate of SVR [2]. This led to the concept of weight-based dosing of RBV, which was later confirmed in large multicenter studies both for PEG-IFN-α2b [3] and PEG-IFN-α2a [4]. As a result of the differences in the design of phase 3 studies for the two PEG-IFN-α [2, 4, 5] molecules, the approved doses of weight-based RBV were different: <65 kg = 800 mg, 65-85 kg = 1000 mg, 85-105 kg = 1200 mg, >105 kg = 1400 mg for PEG-IFN-α2b; ≤75 kg = 1000 mg, >75 kg = 1200 mg for PEG-IFN-α2a [6]. However, in these registration trials, the rates of SVR achieved with the two PEG-IFN-α agents were similar.

The stage was set to compare the two agents head-to-head. Over the past few years a number of studies have compared PEG-IFN-α2a to PEG-IFN-α2b directly, and most of this experience is appropriately synthesized in the meta-analysis of Alavian *et al.*, appearing this month in *Hepatitis Monthly* [7]. From the seven clinical trials that these authors selected for their study, three deserve special mention given their high quality and the number of patients included. In these trials, weight-based RBV played a major role in defining the correct comparison between the two subtypes of PEG-IFN-α.

The IDEAL study was a pharmaceutically-driven initiative to answer the PEG-IFN-α question in

*** Correspondence:**
Elizabeth Jenny Heathcote, M.D., F.R.C.P., F.R.C.P.C.
Liver Centre, Toronto Western Hospital, University Health Network, 399 Bathurst St, 6B Fell Pavilion, Room 172, Toronto, Ontario M5T 2S8, Canada.

Tel: *+1 416 603 5800 ext. 2776*

Fax: *+1 416 603 6281*

E-mail: *jenny.heathcote@utoronto.ca*

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patients with genotype 1 infection. IDEAL had many strengths, including generally sound methodology and an enormous number of patients; however the study suffered from one major design flaw. The decision to use the approved weight-based RBV doses for each PEG-IFN-α rather than a common dosing strategy for the study, made a direct comparison of the groups difficult. As can be observed in Fig. 1

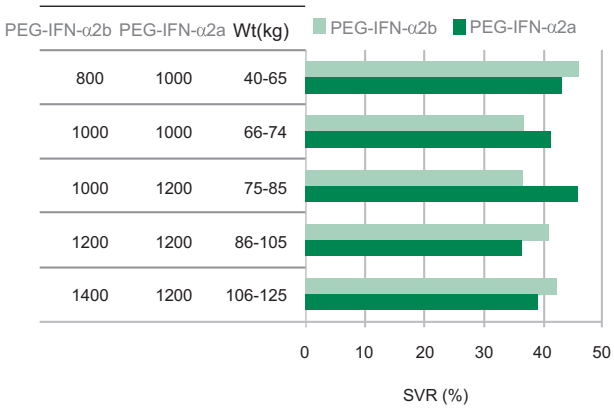

Figure 1. Ribavirin dose (mg) and sustained virologic response (SVR) in IDEAL study according to body weight (Wt). The table to the left shows the ribavirin doses according to each Wt category, and the bars to the right depict the percentage of SVR attained in each Wt category for both peginterferon-α2b (gray bars) and -α2a (black bars).

(which excludes the arm with 1 μg/kg/wk of PEG-IFN-α2b), there were 3 unbalanced subgroups according to RBV dosing (accounting for 52% of the study population), and 2 comparable subgroups. The study found an overall non-significant difference in SVR of 1.1% favoring PEG-IFN-α2a. The authors were quick to point out that much of this difference related to the ~10% SVR advantage of PEG-IFN-α2a in the subgroup of patients weighing 75-85 kg, which they attributed to the higher RBV doses received by this group of patients in the PEG-IFN-α2a arm [8]. However, in the lowest weight category (<65 kg) the dose of RBV was higher in the PEG-IFN-α2a arm, yet the SVR rate did not attain a significantly higher rate in those treated with PEG-IFN-α2b. It is very unfortunate that the sponsors and authors of the IDEAL trial did not use similar regimens of RBV in all arms of the trial, particularly because is it unlikely that another study of similar size will be ever conducted to address potential differences in efficacy of the two PEG-IFN-α preparations. It is noteworthy that despite being sponsored by the makers of PEG-IFN-α2b, the RBV dosing schedule actually gave the overall advantage to the patients on PEG-IFN-α2a because of the large number of patients in the 75-85 kg weight category. In the study by Rumi *et al.*, with a similar design and a similar unequal ribavirin-dosing strategy, a statistically significant benefit was seen with treatment with PEG-IFN-α2a. The authors did not report the breakdown of weight categories and therefore it is difficult to know if there was an advantage in terms of RBV dose for either group [9].

The other recent head-to-head comparison of PEG-IFN-α2a and PEG-IFN-α2b approached the same question, but used similar doses of RBV for both arms (<75 kg= 1000 mg, ≥75 kg= 1200 mg). Ascione *et al.* found that patients with genotypes 1/4 treated with PEG-IFN-α2a had a 15% higher chance of achieving an SVR when compared to those receiving PEG-IFN-α2b (55% *vs.* 40%, p=0.04). The percentage of gain in response was similar in patients with genotype 1/4 than in genotype 2/3. One unexplained result from this study was the very poor compliance and high discontinuation rate in the PEG-IFN-α2b arm. Only 22% of patients with genotype 1/4 treated with PEG-IFN-α2b kept to the 80/80/80 rule and 14% stopped therapy early, compared to only 3% in those treated with PEG-IFN-α2a [10]. Most other studies have shown similar tolerance between the agents. This discrepancy aside, the trial was otherwise well designed and carried out, and is perhaps the most robust evidence suggesting that PEG-IFN-α2a has superior efficacy, as found in the meta-analysis of Alavian *et al.*, and in the meta-analysis of the Cochrane Hepato-Biliary Group [11].

Meta-analyses bring together data from studies that may differ in design, setting and patient population. Heterogeneity is expected to arise, and it was correctly identified and adjusted for using appropriate statistical methods in the meta-analysis in this issue of *Hepatitis Monthly* [12]. But, can statistics correct the inconsistency in the RBV doses or the unexplained drop-out? It is our opinion that they cannot. The work of Alavian *et al.* suggesting the superiority of PEG-IFN-α2a is important but flaws in all of the most important trials make it difficult to draw firm conclusions. This highlights the importance of good trial design when setting out to answer important clinical questions. Simple questions may be followed by simple answers, but only if the groups start out on an equal footing. It is for this reason that the battle of the pegylated alpha interferons remains an unresolved Clash of the Titans.

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Alavian *et al.* reply:

We are really thankful to Dr. Andrés Duarte-Rojo *et al.* for his kind attention and constructive comments. We completely agree with the authors regarding some existing limitations in methodology and lack of homogeneity among ribavirin treatment protocols across studies, and even treatment arms inside each single study. However, there are some very important points to which we must give our attention. Our sensitivity analysis did not show any significant difference by excluding any single study. The two forest plots provided below show pooled ORs of SVR for PEG-IFN-α2a over 2b. By excluding the study of McHuchison [1], these OR increases can be justifed by a discrepancy between the ribavirin doses in two treatment arms. As presented in forest plot 2, the pooled ORs remained constant, even after discarding Ascion *et al.*'s study [2] with suspicious dropouts among the PEG-IFN-α2b group. Based on this sensitivity analysis, we can conclude that the clash of the Titans is going to end up with the victory of Perseus over the Kraken.

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