

Platelets Help in the Difficult Task of Deciding when and who should Receive Antiviral Treatment

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Editorial

Over the last decades we have witnessed a real revolution in the treatment of viruses. It started with the development of antiretrovirals to eliminate the Human Immunodeficiency Virus (HIV) responsible for a global health crisis. HIV continues to be a major global problem, and according to statistics 38.1 million people have become infected with HIV and 25.3 million people have died of AIDS-related illnesses [1]. Now over six distinctive drug classes of antiretrovirals and as many as 40 HIV commercially available medicines are available to address HIV infection. Although the World Health Organization (WHO), governments around the world, and private agencies have joined efforts to expand access to antiretroviral therapy, only half of people are receiving treatment, and not all are resulting in success [1]. Based on surveillance data it has been estimated that 28% of the patients receiving ART did not achieve undetectable viral loads [2]. Even worse, in certain groups (alcohol users and drug addicts) these rates are even higher. These findings are of concern when considering that the monthly cost of an antiretroviral goes from \$400 to \$4,097.78 per month depending of the selected regimen [3].

Another virus is joining the burden of health care costs, the hepatitis B and C virus. It is estimated that approximately 150-180 million people in the world are living with chronic hepatitis [1,2]. Of them, approximately a third (20%-40%) will develop cirrhosis or hepatocellular carcinoma and die [4]. Fortunately, anti-viral treatment for viral hepatitis is now available to achieve viral suppression. Similar to HIV, combination therapy represents the gold standard. At the beginning the standard of care for Hepatitis C infection was a combination of pegylated interferon and ribavirin [5]. Unfortunately, this treatment not only was accompanied by severe side effects, it was effective in only half of the cases. Last year, the national guidelines included new anti-virals that significantly improved viral suppression rates [5]. Yet, the new treatment protocols are prohibitively priced (\$80,000 - \$120,000) and many need two courses of treatment, because they do not yield sustained virologic response. Unfortunately, even when undetectable viral loads are achieved, the risk of hepatocellular carcinoma is not completely abolished [4].

The cost for viral hepatitis B is similar, but the results are even less promising for the 240 million people infected worldwide. Interferon and pegylated interferon virological response are only reached in approximately 35% of the cases [6]. NRTIs are more effective at reducing hepatitis B viral loads. Responses are even grimmer in the case of co-infections with HIV, which are very common globally.

Considering that even rich countries cannot afford treatment for all, and given that a sizable proportion of patients will fail treatments, health care providers and policy makers need to take major decisions based on: a) who will benefit the most; b) factors associated with treatment outcomes; and c) the optimal tests to monitor progress. The tool (s) selected need to be affordable and widely available when considering that logistical and financial barriers are much higher in resource-limited countries.

Notably, many of the affordable, routinely available, noninvasive models/algorithms that are currently available include platelets. Studies have pointed out for years that there is a close interaction between viral infections and platelets [4]. In the beginning, thrombocytopenia was considered a marker of advanced disease, but the old paradigm has been falling with the increasing number of studies showing that thrombocytopenia is, in many cases, the first sign of a viral infection [5]. For others, platelets were one of the many bystanders that were destroyed in the war between the virus and the immune system. Now there is no doubt about the direct involvement of platelets in the fight with the virus, and its role in the inflammatory response. Therefore, scientists now include platelet-to-lymphocyte ratios (PLR) as a marker of systemic inflammatory responses [4].

Thrombocytopenia has been found in as many as 50% of people living with HIV, but is observed during primary HIV infection in approximately 10% of patients [7]. Our group, along with others, have repetitively demonstrated that persistent thrombocytopenia among those receiving antiretroviral therapy is associated with higher viral loads compared to non-thrombocytopenic controls [7,8]. As a result, patients with thrombocytopenia face significantly higher risk of death than those with normal counts [7-10]. Findings are not unexpected, given that platelets carry kinocidins, β -defensins, and microbicidal proteins important for antiviral host defense [7-10].

Konerman, Yapali, and Lok did a systematic review of the literature to identify the best predictors and predictive models of disease progression for patients with hepatitis C in need of early treatment and intensive monitoring [11]. The authors concluded that baseline platelet count was the most consistent independent predictor of clinical outcomes (significant on multivariate analysis in six of 13 studies) [10].

The likelihood of a sustained virological response is the most important outcome for health care providers and authorities in the decision to provide therapy for hepatitis C. In this regard, Mauss et al. established that genotype baseline viral load, age, GGT, and platelet levels predict treatment success with peg-interferon plus ribavirin [12]. Ito et al. constructed another simple formula to determine, at the patients' first/second visit, the probability of response to Peg-IFN alpha2b and RBV combination therapy for genotype 1 hepatitis C patients [12]. The formula was based on: male gender (point 2)+HCV RNA load<1000 KIU (3)+ platelet counts $\geq 15 \times 10^3/\text{mm}^3$ (1)+age<60

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(1) and was able to predict who would have a sustained virological response in 70.2% of the cases [13]. McCombs et al. conducted another study to determine what laboratory tests could be used to define a “trip wire” or a point at which a clinician should start treatment [14]. Again, platelets were among the list laboratory parameters that correlated with increased risk of liver-related events. They also confirmed that platelet reduction diminished the effectiveness of antiviral treatment.

Although hepatitis C infection is mostly characterized for its progression, the course of hepatitis B infection is characterized by fluctuations in both viral replication and disease activity. Notably these fluctuations correlate with platelets, as the prevalence rates of thrombocytopenia varied between 10% in those with inactive Hepatitis B infection, and 17% in active hepatitis B patients [15]. In addition, platelets are also independent risk factors of hepatocellular carcinoma in patients with drug-resistant hepatitis B [16].

In summary, data highlights the importance of platelets as a prognostic factor of treatment responses and survival in patients infected with viruses. However, it is not fully understood why and how platelets are such effective markers of disease and treatment prognosis. Clearly, there is a need of further research to better understand the mechanisms underlying such a close relationship.

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