EBioMedicine 36 (2018) 7–8

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Immunoglobulin replacement therapy targeting the BCR in chronic lymphocytic leukemia

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Chronic lymphocytic leukemia (CLL) is characterized by an increase in the frequency of infections, which are a main cause of morbidity and mortality [1,2]. In CLL, immune reactions are bidirectional, with CLL cells using several mechanisms to modify and immunosuppress the normal, non-leukemic elements of the immune system, and at the same time these non-leukemic elements attack the leukemic cells [2,3]. An example of the former is hypogammaglobulinaemia, which results from a progressive reduction in immunoglobulin levels and deterioration of the immune system as the leukemic clone expands and the disease progresses [1,2]. Efforts have been made to decrease this humoral and cellular decline and the infections they lead to by using vaccines, replacing immunoglobulins, and administering prophylactic antimicrobials and soluble growth factors.

In *EBioMedicine*, Spaner and coworkers present a study describing clinically and biologically important data indicating the effects of soluble immunoglobulin during the disease course and the effect of immunoglobulin replacement therapy (IgRT) *in vivo* and *in vitro* [4]. They emphasize not on the importance of Ig to control infection but to control CLL cells and the disease itself. In a set of serial samples from untreated patients, the authors observed that aggressive disease was associated with a faster drop in the humoral immune status, correlating the deterioration with an increase in several molecules in the serum including TNFα and β2microglobulin (B2M). Next is presented the key finding of this study: patients receiving IgRT that increases IgG levels over 9 g/L show evidence of disease control and reduction of TNFα and B2M levels. This observation is explained in part by their *in vitro* results where soluble IgG in the culture medium reduces CLL B-cell activation and survival.

Ig levels have been previously associated with the prognosis of CLL patients [1,2], but in this manuscript the authors correlate the velocity of humoral immune response deterioration with the aggressiveness of the leukemia. Moreover, the authors present *in vitro* data suggesting that disease control by IgG is induced by blocking B-cell receptor (BCR)-mediated signaling and decreasing CLL B-cell survival in a subset of patients. The authors propose that the mechanism underlying this occurs *via* the inhibitory receptor FcγRIIb (CD32B). This is the only FcγR on CLL cells, and interestingly low density on the surface of leukemic cells is associated with worse prognosis [5]. Thus, in addition to the proposed cytokine profile in the manuscript, unresponsiveness by some CLL samples could be due to the low density of the FcγR or to other factors that still need to be unraveled. In addition to the direct effect on the BCR signaling, several immunomodulatory effects of antibodies in the IgRT have been described that could also contribute to the effect observed *in vivo* [6], and that should be considered in future mechanistic experiments.

Hypogammaglobulinaemia is not a criterion to start treatment in CLL patients [7], and therapy does not appear to have a great benefit in restoring it [2,3,8,9]. Moreover, several reports support the use of IgRT to reduce the risk of bacterial infections in patients with severe hypogammaglobulinaemia, although IgRT does not significantly protect against viral or fungal infections and has not been shown to improve survival duration [1,2]. However, IgRT only provides IgG, and since CLL patients are often also deficient in other immunoglobulin isotypes [1,2], introduction of IgM and IgA might boost efficacy leading to control of a broader set of infections. Unfortunately, convenient access to these isotypes has not been achieved, although groups are working in optimizing the formulation and chemistry [6]. Finally, although the etiology of the hypogammaglobulinaemia is not completely understood, it is known that several factors important for the promotion of plasma cells and Ig production are altered in CLL patients, including reduced T-cell function and increased levels of TGF-β [2,3]. Restoration of normal B-cell function and differentiation could also help the return to normal Ig levels and control of CLL.

To conclude, based on the new data presented by Spaner et al. and those reported by Besa et al 35 years ago [10], IgRT might represent a new CLL therapy, at least in a group of patients. However, there is still not enough evidence to repurpose IgRT to treat CLL, and randomized clinical trials are necessary. In addition, limitations in optimal and adequate product production, an inability to identify those patients that will profit the most from replacement, and the yet unknown cost/benefit ratio are major handicaps. Nevertheless since the immune system not only protects against infections but also against cancer, the continuous study of CLL cell biology and how this impacts on normal immune system function have the potential to improve present therapies and unravel a cure for CLL.

Disclosure

The author declares no conflicts of interest.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.08.045.
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https://doi.org/10.1016/j.ebiom.2018.09.008

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