Combination treatment strategies to eradicate CLL, allowing for treatment discontinuation, would therefore be desirable, and clinical trial efforts with this goal are currently ongoing (eg, NCT02401503).

In summary, the study by Byrd et al1 highlights the high activity of obinutuzumab as a single agent in patients with CLL and corroborates earlier trial experience showing that there is a dose response with anti-CD20 mAbs in CLL.2,3 Thus, despite the limitations of the trial by Byrd et al, which does not provide a robust rationale for use of higher-dose obinutuzumab in the short-term because of the lack of any major PFS benefit, we should not discard the possibility of a revival of higher-dose obinutuzumab in the future, for example in combination strategies in which achievement of deep remissions is the goal.

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Rebooting autoimmunity with autologous HSCT

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Autologous hematopoietic stem cell transplantation (HSCT) is increasingly used for severe autoimmune and inflammatory diseases, but the mechanisms involved have yet to be elucidated. In this issue of Blood, Delemarre et al report their findings in both animal and human models which provide insights into restoration of functionality and diversity within the regulatory T-cell (Treg) compartment following HSCT.1

The findings of Delemarre et al come some 25 years after their fellow Dutch investigator, the late Prof Dirk van Bekkum (1925-2015), started to lay down the preclinical foundations for using HSCT in autoimmune diseases with an elegant series of experiments.2,3 Over the last 2 decades the field has developed gradually in the clinical setting in a variety of diseases. International databases now have several thousand patients and there is an increasing evidence base of large series and randomized controlled trials to support the use whether obinutuzumab is best used alone or in combination. Cross-trial comparisons have many limitations, but the 18-month PFS with standard-dose obinutuzumab (59%) reported in the article by Byrd et al appears shorter than what was reported for obinutuzumab plus chlorambucil (~80% at 18 months),2 and the authors argue that this may favor the use of higher-dose obinutuzumab in which the PFS at 18 months was more similar to that in the data for the chlorambucil combination. However, at later time points, the PFS curves of the 2 obinutuzumab dose regimens merged (see Figure 2 in the article by Byrd et al that begins on page 79), and there was no significant PFS benefit that favored the higher-dose obinutuzumab or that would change current dosing practice. These data indicate that higher-dose obinutuzumab has only limited advantage; it achieves deeper remissions which, after finishing the 6 months of treatment, do not translate into any major PFS benefit when compared with standard-dose obinutuzumab. Accordingly, current trials use standard dosing of obinutuzumab and favor obinutuzumab maintenance strategies over the higher-dose obinutuzumab used in combination trials (see table).

The most obvious combination partners for obinutuzumab are the standard CIT regimen (fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab) in which rituximab is replaced by obinutuzumab to achieve more complete and/or durable responses. We also need to take into account that the use of CIT in CLL patients, especially in patients with high-risk disease, is declining because of superb data and broader availability of kinase inhibitors targeting B-cell receptor signaling (ie, the Bruton’s tyrosine kinase inhibitor ibrutinib,9 the phosphatidylinositol 3-kinase delta inhibitor idelalisib,10 and the B-cell lymphoma 2 antagonist GDC-0199). These agents are changing the current landscape of CLL therapy; the high number of obinutuzumab trials in combination with novel agents (see table) reflects this ongoing major change in clinical practice. With the addition of these new effective agents, including obinutuzumab, to our therapeutic armamentarium, long-term disease control can be achieved in more and more CLL patients, even those with high-risk features. Conversely, the high costs of long-term treatment with these agents to maintain remissions will increase the burden on our health care systems and our patients.
Successful autologous HSCT leads to a renewed and more diverse Treg TCR repertoire. (A) Patient with severe autoimmune disease pre- and postautologous HSCT. The pie charts show TCR β-chain sequencing results in Treg and non-Treg cells collected from a patient with severe autoimmune disease before and after autologous HSCT. N represents the number of different TCR sequences per sample and Di indicates diversity (0 = no diversity, 1 = maximal diversity). Changes in Di before and after HSCT are also shown in the graph. (B) Four healthy controls (HC). For comparison, TCR β-chain sequencing results in Treg cells from 4 HC are shown in a similar fashion. The figure has been adapted from Figure 4 in the article by Delemarre et al that begins on page 91. Professional illustration by Patrick Lane, ScEYEnce Studios.

Response to autologous HSCT also varies within the same disease and has been related to patient-related factors, such as stage of disease, and there is scope for improving responses and selecting the best patients. In MS, restoration of TCR diversity has been reported as a potential predictor of clinical response.9 Outcomes in juvenile idiopathic arthritis have also been related to the degree of thymic processing in reconstituting the T-cell compartment.10 TCR characterization may enable monitoring of pathogenic or protective T-cell clones following autologous HSCT for autoimmune diseases. Whether more specific assessment of Treg TCR diversity, as described by Delemarre et al, is a better predictor remains to be established. It is possible that such testing may assist with the selection of patients most likely to respond from HSCT and in identifying patients who may benefit from early interventions, including low-dose maintenance or salvage treatments or additional cellular therapies. However, in the current study, despite the reasonable logic, no benefit was achieved through additional Treg infusions. Clearly, this area requires more investigation.

Mechanistic studies may have been historically challenging to coordinate across a range of autoimmune diseases, perhaps because autologous HSCT has most often been used sporadically as an exceptional treatment in refractory patients, and sometimes as an emergency salvage procedure. With a greater evidence base the numbers of patients being treated are increasing substantially in some diseases, such as MS. Moreover, patients are being treated at an earlier stage in their disease, when both end organ damage and immune defects are potentially more reversible. Recent publication of international biobanking guidelines may facilitate access of samples to laboratories for specialized immune reconstitution studies before and after HSCT.6
Identifying risk factors for B-cell lymphoma

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In this issue of Blood, Melenotte and colleagues provide an interesting and provocative analysis of a potential novel risk factor for B-cell non-Hodgkin lymphoma (NHL).¹

This is one of the first studies to focus on Coxiella burnetii (the infectious agent associated with Q fever) as an inciting factor for lymphomas. Building on the identification of an incident case, the authors examined the incidence of lymphoma among individuals with Q fever. These analyses provide clinically meaningful insights that may aid in the identification of a novel risk factor for diffuse large B-cell lymphoma (DLBCL) and other B-cell NHLs and support the development of a comprehensive understanding of factors associated with lymphoma incidence. Utilizing a French National Referral Center for Q fever database of 1468 consecutive patients diagnosed from 2004 to 2014, and accounting for differences in age and sex distribution between the Q fever cohort and the general French population, the authors identified an increase in the incidence of DLBCL and follicular lymphoma (FL) in individuals who had Q fever compared with the general population, with standardized incidence rates of 25.4 (95% confidence interval [CI], 11.4-56.4) and 6.7 (95% CI, 0.9-47.9), respectively. Moreover, a diagnosis of Q fever with a persistent focal infection was noted to have a greater risk of lymphoma with a hazard ratio of 9 over the period of observation. For these analyses, acute Q fever was defined by the association of clinical symptoms (fever, hepatitis, and/or pneumonia) with the serological criteria of a phase 2 immunoglobulin G (IgG) titer ≥200 and a phase 2 IgM titer ≥50, seroconversion or a positive polymerase chain reaction (PCR), and no endocarditis. Supporting these epidemiological data were findings that interleukin–10 production was significantly increased in patients with lymphoma, particularly those with Q fever. Moreover, C. burnetii was detected in CD68+ macrophages within lymphoma and lymphadenitis tissues in patients with and without lymphoma, but infection was localized in plasmacytoid dendritic cells in lymphoma tissues only providing early evidence for a possible pathway to lymphomagenesis. Although the selection process for assembly of the cohort of patients and serological samples for the Q fever database may introduce biases that could influence the strength of association between C. burnetii/Q fever and the incidence of B-cell NHLs, this analysis provides insight for a new infectious disease linked to lymphoma. Further validation of these observations would add Q fever to the list of infectious agents such as Epstein-Barr virus, Helicobacter pylori, and hepatitis C infection involved in the pathogenesis of B-cell lymphomas.

These findings must be considered in the context of numerous other analyses examining infectious and other risk factors for B-NHL, most notably the recent large international pooled InterLymph Subtypes Project.²,³ The International Lymphoma Epidemiology Consortium (InterLymph) was formed in 2001 to perform pooled case-control studies that maximize statistical power to identify common as well as distinct risk factors among NHL subtypes. This group has identified numerous demographic, medical history, environmental, and genetic risk factors for lymphoma, exposing the common threads and heterogeneity in etiology across NHL subtypes. Of relevance to the present study, the subtype study of DLBCL performed a pooled analyses of 4667 cases and 22 639 controls from epidemiological studies in Australia, Europe, and North America and...
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