Proteasome inhibition: a new therapeutic option in lupus nephritis?*

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Antinuclear auto-antibodies are a hallmark of systemic lupus erythematosus. Based on the characteristics of these auto-antibodies (somatic mutation, restricted use of certain VH and VL genes, high avidity IgG antibodies, common idotypes), lupus is regarded as an auto-antigen-driven T-cell-dependent autoimmune disease [1]. It is generally assumed, however, that the produced auto-antibodies are pivotal for the development of tissue lesions, and hence also B cells are necessary for disease development. Indeed, MRL/lpr lupus mice, which due to a certain genetic manipulation lack B cells, develop neither glomerulonephritis nor vasculitis [2]. Therefore, in lupus, B cells represent a major target for treatment. Cyclophosphamide, an effective, although toxic, drug in the treatment of lupus nephritis depletes B cells (but also other cell types) and quickly suppresses auto-antibody formation. More recently, a number of new treatment options became available in lupus, all directed at the B cell [3]. These therapies have different mechanisms to influence B-cell function: (i) depletion by anti-CD20 antibodies (rituximab, ocrelizumab); (ii) reduction of anti-DNA titres (LJP394/abetimus); (iii) blockade of T-cell co-stimulation (CTLA4-Ig: abatacept and belatacept) and (iv) blockade of B-cell stimulation via CD40 or the cytokine BLys (betalumab or atacicept).

Experience with these B cell-targeted therapies has taught that treatment efficacy goes beyond the reduction of auto-antibody levels and is in part due to silencing of B cells. This also affects other B-cell functions important for development and persistence of autoimmunity. However, these therapies hardly influence long-lived plasma cells. These long-lived plasma cells are important in lupus, because they represent a major fraction of the auto-antibody-producing B cells. Since they are a difficult target to treat, they are important for the perpetuation and flares of the autoimmune disease. Recently, Neubert and colleagues have described a new approach, which also attacks these long-lived plasma cells [4]. They evaluated the effect of bortezomib (BTZM) on lupus nephritis in two mouse models of spontaneous lupus namely the (NZBxNZW)F1 and MRL/lpr model. BTZM has been used successfully in relapsing or refractory multiple myeloma [5]. BTZM is an inhibitor of the 26S proteasome, thereby inhibiting the degradation of misfolded, defective and regulatory proteins. This inhibition leads to the activation of the terminal unfolded protein response (UPR) that induces apoptosis of the cell. Susceptibility of cells for BTZM is correlated with the extent of protein production, and in myeloma B cells, with the extent of Ig production [6]. This finding raised the idea whether this might also be true for non-malignant B cells with a high Ig production. This was indeed the case. BTZM (0.75 mg/kg body weight given twice at 0 and 36 h) in ovalbumin-immunized BALB/c mice led after 48 h to a reduction of B cell numbers in the spleen of 60% and in the bone marrow of 80%. In the (NZBxNZW)F1 lupus strain, BTZM induced after 48 h a 96% reduction of splenic B cells and 88% of bone-marrow B cells and an almost complete disappearance of anti-dsDNA-producing B cells. With proliferation markers it was determined that both short- and long-lived plasma cells were depleted. This effect of BTZM on long-lived plasma cells was much more efficient than that achieved by dexamethasone or cyclophosphamide. These two latter drugs also depleted T cells, macrophages and dendritic cells in contrast to BTZM. As in tumour cells, BTZM exerts its action in B cells by creating a pro-apoptotic milieu by activating the terminal UPR and by inhibiting activation of the anti-apoptotic NFκB. Of potential clinical relevance is the observation that BTZM given twice weekly intravenously in a dose of 0.75 mg/kg body weight for 10 months prevented formation of anti-dsDNA antibodies, proteinuria and histological signs of glomerulonephritis and prolonged survival in (NZBxNZW)F1 mice. In a subsequent study, BTZM treatment proved also effective when started in (NZBxNZW)F1 mice that already had anti-dsDNA antibodies and proteinuria. BTZM reverted anti-dsDNA antibody formation and proteinuria. Similar results were obtained in another murine lupus model, the MRL/lpr strain. To evaluate overall
immunosuppression, immunizations with T-cell-dependent and T-cell-independent antigens were performed. During BTZM treatment, the response to T-cell-dependent antigens was severely decreased but was normal if immunization was carried out 5 days after cessation of BTZM treatment. The response to T-cell-independent antigens was unimpaired, even during BTZM treatment, consistent with the observation that BTZM does not affect marginal zone B cells, which are responsible for this IgM response.

What are the clinical perspectives of these findings with BTZM in spontaneous lupus mouse models? In the recent years, experience has been obtained with BTZM in the treatment of patients with multiple myeloma, mantle cell lymphoma and certain solid tumours [7].

However, the doses used in these clinical studies were 1–1.5 mg/m² per administration. In the lupus mouse studies, much higher dosages were used of 0.75 mg/kg body weight. Although it is very difficult, if not impossible, to extrapolate dosing in mice to patients, it remains to be determined whether dosages used in multiple myeloma patients are also effective in lupus patients. Also from the experience in multiple myeloma patients, it is clear that BTZM has serious adverse events [5]. Early discontinuation because of side effects was necessary in 37% of the patients. These side effects include polyneuropathy (36%), thrombocytopenia (35%) and gastrointestinal complaints (57%).

So it remains to be determined whether this high incidence of side effects precludes the use of BTZM in lupus nephritis because recently alternatives for cyclophosphamide became available like MMF and anti-CD20 with a much better tolerability.

Therefore, at present it is difficult to predict whether BTZM will become a therapeutic option in the treatment of severe lupus. A potential cohort of patients could form those patients in whom stem cell transplantation is considered because of the severity and uncontrollable nature of the disease. In contrast to stem cell transplantation [8,9], BTZM has the capacity to attack long-lived plasma cells [4].

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References

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