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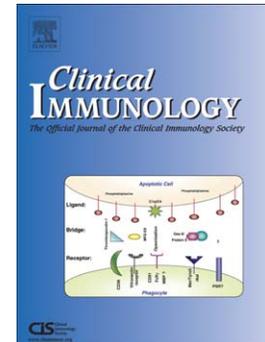
A Role for Plasma Cell Targeting Agents in Immune Tolerance Induction in
Autoimmune Disease and Antibody Responses to Therapeutic Proteins

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Abstract:

Antibody responses to life saving therapeutic protein products, such as enzyme replacement therapies (ERT) in the setting of lysosomal storage diseases, have nullified product efficacy and caused clinical deterioration and death despite treatment with immune-suppressive therapies. Moreover, in some autoimmune diseases, pathology is mediated by a robust antibody response to endogenous proteins such as is the case in pulmonary alveolar proteinosis, mediated by antibodies to Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF). In this work, we make the case that in such settings, when the antibody response is high titered, sustained, and refractory to immune suppressive treatments, the antibody response is mediated by long-lived plasma cells which are relatively unperturbed by immune suppressants including rituximab. However, long-lived plasma cells can be targeted by proteasome inhibitors such as bortezomib. Recent reports of successful reversal of antibody responses with bortezomib in the settings of ERT and Thrombotic Thrombocytopenic Purpura (TTP) argue that the safety and efficacy of such plasma cell targeting agents should be evaluated in larger scale clinical trials to delineate the risks and benefits of such therapies in the settings of antibody-mediated adverse effects to therapeutic proteins and autoantibody mediated pathology.

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A Role for Plasma Cell Targeting Agents in Immune Tolerance Induction in Autoimmune Disease and Antibody Responses to Therapeutic Proteins

In the past few years, there have been reports of successful reversal of antibody and autoantibody responses with the administration of the plasma cell targeted drug bortezomib. We take note of two reports in which treatment of patients with antibody mediated pathology in the settings of ERT for infantile-onset Pompe disease and TTP with bortezomib [1,2] successfully reversed the antibody and autoantibody responses, respectively, leading to significant clinical improvement. In both settings the antibody response had been sustained in the face of treatment with immune suppressive agents including rituximab, the monoclonal antibody (mAb) which targets CD20 expressing cells, thereby depleting mature and memory B cells, but not the long lived plasma cells (CD20 negative) responsible for high titer and sustained antibody responses (Fig 1).

Reviews [3,4] of the use of bortezomib or potentially, other proteasome inhibitors in autoimmune disease and antibody mediated allograft rejection, proposing its evaluation in autoimmune myasthenia gravis and SLE, further highlight the potential of therapeutics targeting long-lived auto- or allo-antibody secreting plasma cells in relevant pathologic settings (Table 1). Indeed there are a number of diseases in which autoantibodies play a predominant role in pathophysiology such as myasthenia gravis (mediated by antibodies to post-synaptic proteins of the neuromuscular junction) [3], the anti-synthetase syndrome (mediated by antibodies against aminoacyl-tRNA synthetases) [5], pulmonary alveolar proteinosis (mediated by autoantibodies to GM-CSF) [6], and various manifestations of systemic lupus erythematosus (SLE) [7-12]. In each of these cases, successful treatment would appear to rely on eliminating or diminishing the antibody response and induction of immunologic tolerance.

In addition to the damage caused by auto-antibodies in many autoimmune conditions, antibodies formed against the neoantigens in replacement factors are well known to abrogate efficacy in the cases of Factor VIII treatment of Hemophilia A [13] and Factor IX treatment in Hemophilia B [14] and of ERTs in the setting of Lysosomal Storage Diseases (LSDs), such as infantile-onset Pompe disease [15-17], mucopolysaccharidosis type I and II and Gaucher disease [18-19]. The negative impact of antibodies on clinical outcome is clear, for example, in infantile-onset CRIM negative Pompe disease, where disease progresses rapidly and the antibody mediated loss of efficacy of ERT hastens clinical decline and death, while tolerance induction has been shown to prevent or restore the efficacy of ERT in case studies [20-21]. Additionally, the efficacy of highly effective therapeutic proteins such as TNF specific monoclonal antibodies [22], and interferon β [23] may also be compromised by anti-drug antibodies.

Plasma Cell Targeting Agents

Given the considerations above, we believe that it is appropriate to investigate the safety and efficacy of plasma cell targeting agents in larger scale clinical trials that are sufficiently powered to delineate the risks and benefits of such therapies in antibody-

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mediated clinical conditions. Drugs used to treat multiple myeloma, a plasma cell malignancy characterized by proliferation and accumulation of abnormal plasma cells, may provide clues for drugs that could potentially be explored for plasma cell targeting. The proteasome (24), plays a major role in cell cycle progression and immune responses. The immunoproteasome, a class of the proteasome mainly expressed in cells of lymphoid origin, plays an important role in antigen processing and the immune response [24, 25].

Proteosome Inhibitors
As noted above, the proteasome inhibitor bortezomib ameliorated high titered and sustained antibody responses to ERT in some infantile-onset Pompe disease patients [2]. In addition, bortezomib was shown to be beneficial in a number of case reports of TTP [1, 26, 27, and 28]. In the majority of nonfamilial TTP cases, autoantibodies against ADAMTS13, a metalloproteinase that cleaves vonWillebrand factor, are associated with the disease, and patients have very low or no ADAMTS13 activity. In all instances described in the case reports, patients failed to respond to therapeutic plasma exchange or to treatment with other agents, such as rituximab, despite depletion of CD20-positive B cells [27]. Treatment with bortezomib progressively normalized hemoglobin levels and increased activity of ADAMTS13 in various degrees, up to 109% in one case [28]. Furthermore, bortezomib treatment drastically reduced the titer of anti-ADAMTS13 antibody. A similar effect of bortezomib has been observed in SLE. Bortezomib reduced plasma cell numbers and immunoglobulin levels in SLE patients, with greater reduction in disease-associated autoantibodies (anti-dsDNA), ameliorated specific SLE disease scores and successfully controlled autoimmune hemolytic anemia [29, 30]. Furthermore, in animal models of the disease, bortezomib protected mice from nephritis, by reducing the levels of anti-dsDNA, immunoglobulin deposition in kidneys, and proteinuria [31-33]. The reduction in autoantibody levels and demonstration of disease amelioration indicate the need for further studies to evaluate the activity of bortezomib in managing autoimmune diseases.

In addition to bortezomib, there are two other approved proteasome inhibitors in the US, carfilzomib and ixazomib [34, 35]. Proteasome inhibitors are thought to inhibit proliferation and induce apoptosis of target plasma cells, malignant or non-malignant, via inhibition of mediators of cell-cycle progression [36]. Malignant cells appear to be more sensitive to proteasome inhibition than are normal cells [37].

While bortezomib has other known risks such as immune suppression and neurotoxicity, it is notable that reversing an ongoing antibody response in infantile-onset Pompe Disease required fewer cycles of bortezomib than were given in the setting of new onset or refractory, relapsed multiple myeloma [2] [38, 39]. Carfilzomib is an irreversible inhibitor and binds to a different site than bortezomib on the proteasome [34]. Due to carfilzomib's more selective activity (on the 20S proteasome), it may have decreased potential for adverse effects compared with bortezomib [34]. However, neither carfilzomib nor ixazomib have been explored in immune tolerizing regimens while bortezomib has some limited experience in this setting. Additionally, the safety of these agents is particularly limited in children.

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Monoclonal antibodies

Two novel monoclonal antibody products were approved in the US in 2015 for the treatment of multiple myeloma: daratumumab which targets CD38, and elotuzumab which is directed against signaling lymphocytic activation molecule F7 (SLAMF7).

Daratumumab(accelerated approval)

CD38 is expressed in relatively high levels on malignant plasma cells in multiple myeloma as well as on normal plasma cells, but at relatively low levels on other lymphoid and myeloid cells (including CD4, CD8, B lymphocytes and NK cells) and in some tissues of nonhematopoietic origin [40, 41]. The mechanism of action of daratumumab in multiple myeloma appears to be via monoclonal antibody binding to CD38-expressing tumor cells resulting in the following: complement-mediated and antibody dependent cell mediated cytotoxicity (ADCC); antibody-dependent cellular phagocytosis; apoptosis via FcR cross linking; and inhibition of the enzymatic activity of CD38 to some degree [41].

To date it has shown efficacy in multiple myeloma [41], and thus its approval via an accelerated approval pathway, but given its novelty, the safety experience is very limited. Moreover, there is no significant experience in children. Thus, for these reasons, it may be premature at this time to consider daratumumab for further exploration as a potential agent for immune tolerance induction regimens in the setting of HSAT.

Elotuzumab

SLAMF7 is a glycoprotein that is highly expressed on malignant and normal plasma cells, natural killer (NK) cells, and some other immune cells, with no expression on other normal tissues [42]. It is thought to act in multiple myeloma by binding to the surface of myeloma cells and recruiting and activating NK cells, resulting in the killing of multiple myeloma cells via an ADCC mechanism. SLAMF7 appears to be highly expressed on plasma cells making it a potentially attractive agent for plasma cell targeting for immune tolerance induction and may warrant further pre-clinical exploration. However, similar to daratumumab, elotuzumab has limited safety experience, especially in children.

From Diminished Antibody Response to Immune Tolerance Induction

It should also be noted that reversal of long standing antibody or autoantibody responses may not be sufficient to achieve the ultimate goal of immune tolerance induction defined as the lack of a significant immune response in the face of continued treatment with the therapeutic protein, or ongoing exposure to self antigen in the setting of autoimmune disease, without concomitant immune suppressive agents, conferring long term freedom from treatment with immune suppressive agents. For example, in the infantile-onset Pompe setting in which immune tolerance to the therapeutic protein supervened following elimination of antibodies by bortezomib, the administration of rituximab and

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methotrexate following bortezomib treatment may have been critical in precluding generation of new responses [2]. Regardless, elimination or reduction of the ongoing antibody response is a necessary and critical first step of treatment in such settings. It is worth considering that the success of tolerance induction may be lessened by the presence of an ongoing antibody response as has been observed for tolerance induction to Factor VIII [43] and erythropoietin [44]. Indeed, mechanistic studies have elucidated the positive feedback pathway engendered by robust antibody responses in which immune complexes boost the antigen presenting cell capacity of APCs, furthering the immune response [45].

The case of antibody responses to therapeutic proteins differs distinctly from that of autoimmune diseases in that in the former, the antigen is well defined and the point of introduction controlled. Thus, in this setting, the immune response might be precluded altogether by the use of a short course of rituximab and methotrexate, which prevents generation of long-lived antibody secreting plasma cells from their B cell and plasmablast precursors (20). In contrast, in autoimmune diseases, the antigen or antigens may not be well defined, epitope spreading may have extended the immune response to other targets in the same or other proteins as well as nucleic acids, and at the time point of clinical presentation, the patient's antibody response may already be mediated by long-lived plasma cells. However, the success of B cell depletion by rituximab in eliminating antibody responses in some patients with autoimmune syndromes suggests that such patients have an antibody response that is mediated by short-lived plasmablasts, that a progression from plasmablast to long-lived plasma cell is not efficient, and/or that other factors that drive durable antibody responses (e.g., high levels of interferon) are not present in the disease (Fig 1). Unfortunately, there are currently no unique markers for autoantibodies originating from long-lived plasma cells (e.g., glycosylation signatures). Thus, measurement of immune responses mediated by long-lived plasma cells relies on less direct measures, such as antibody titer and duration of antibody response. Therefore, lack of efficacy of rituximab in such situations should quickly prompt consideration of evaluation of a plasma cell targeted agent, particularly in the setting of progressive disease and clinical decline.

Conclusions

Recent case reports and small case series in which bortezomib has been targeted to pathological antibody responses in several clinical scenarios have provided evidence of clinical improvement in some patients. Such results provide a strong incentive to perform larger scale clinical trials to evaluate the potential efficacy and safety of agents targeting long-lived plasma cells as a component of immune tolerizing regimens for patients with robust antibody responses to therapeutic proteins and in patients with autoimmune diseases with clinical manifestations mediated by autoantibodies. Other plasma cell targeting agents, including other proteasome inhibitors and novel monoclonal antibodies directed at plasma cell surface glycoproteins may also warrant exploration in pre-clinical studies.

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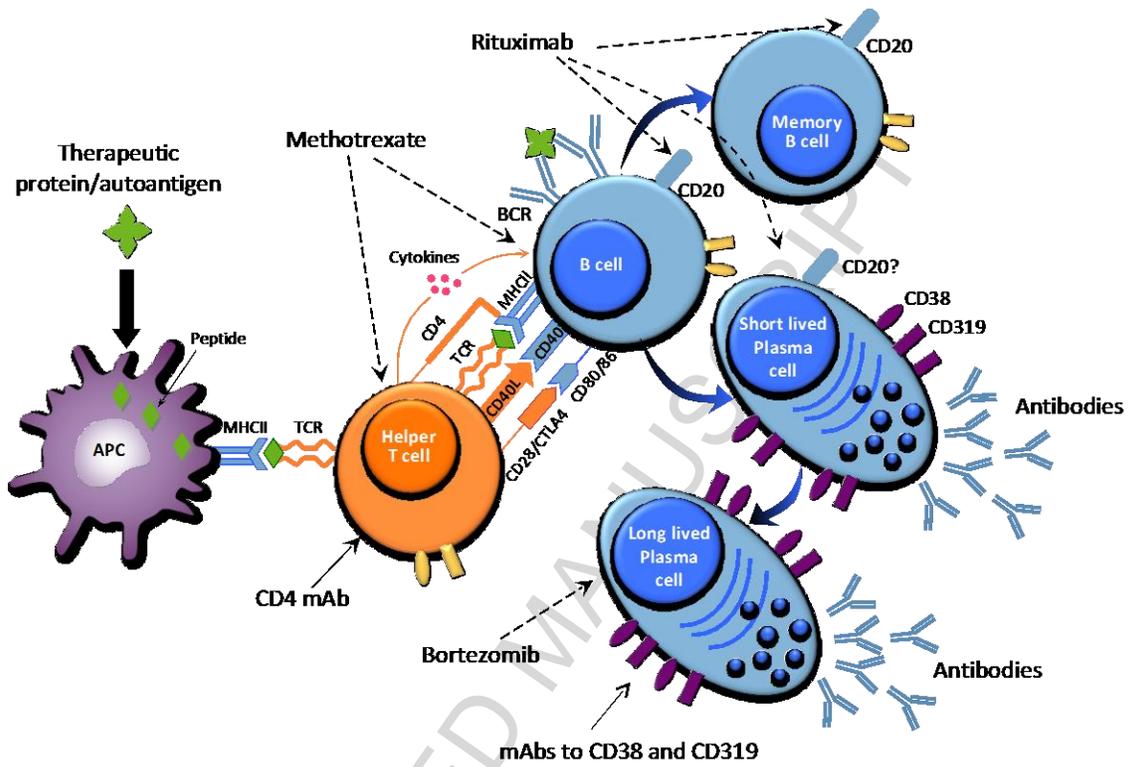
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Fig. 1

Table 1 Autoimmune Diseases with autoantibodies

Diseases with pathogenic antibodies	Diseases with antibodies of unknown significance
SLE: anti-DNA, anti-RNP	Scleroderma: anti-centromere, anti-topoisomerase
RA: RF anti-CCP	Myositis: anti –tRNA synthases
Vasculitis: anti-myeloperoxidase, anti-proteinase 3	Multiple sclerosis: anti-myelin basic protein, anti-MOG
Myasthenia gravis: anti-acetylcholine receptor	Uveitis: Unknown specificity
Hypothyroidism: anti-thyroglobulin	Sjögrens: anti-SSA, anti-SSB
Hyperthyroidism: anti-TSH receptor	Inflammatory bowel disease: numerous
Vitiligo :anti-melanocytes (melanin concentrating hormone receptor (MCHR1)	
Type 1 diabetes: anti-GAD, anti-insulin, anti-islet cell	
Pernicious anemia: anti-intrinsic factor, anti-parietal cell	
Neuromyelitis optica: anti-aquaporin 4, anti-MOG	
Addison's Disease: anti-cytochrome p450	
Primary biliary cirrhosis: anti-pyruvate dehydrogenase	
Paraneoplastic syndromes: numerous	
Limbic encephalitis: anti-GluN1 of the NMDA receptor	
Pemphigus: anti-desmoglein	
Celiac disease: anti-transglutaminase	
Anti- phospholipid syndrome: anti-cardiolipin, anti-β2GP1	
Hemolytic anemia: anti-RBC	
ITP: anti-platelet	

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Highlights

1) Antibodies to life saving therapeutic proteins such as enzyme replacement therapies for lysosomal storage diseases may inhibit product efficacy leading to clinical deterioration and death, as in the case of Pompe Disease.

2) Autoantibodies may mediate pathology in the context of certain autoimmune diseases.

3) High titer, sustained antibody responses may not diminish in response to treatment with immune suppressive agents such as rituximab, methotrexate or Cytoxan. Such responses appear to be mediated by long lived plasma cells which are not targeted by B cell targeting mAbs and resistant to many chemotherapeutic agents

4) High titer sustained antibody responses in the context of autoimmune disease or immune responses to therapeutic proteins refractory to treatment with conventional immune suppressive agents have been dramatically diminished or eliminated by treatment of patients with bortezomib, a proteasome inhibitor, facilitating restoration of immune tolerance.

5) In view of these findings, larger scale studies of proteasome inhibitors in the context of autoimmune disease mediated by robust autoantibody responses should be pursued.

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