

Immunologic Similarities between Selected Autoimmune Diseases and Peanut Allergy: Possible New Therapeutic Approaches

Michael A. Martucci · Stephen C. Dreskin

© Springer Science+Business Media, LLC 2011

Abstract Food allergies are an important medical problem in Westernized countries. Allergy to peanuts is a dramatic example of a food allergy that tends to be particularly severe and long-lived. This article examines food allergy—specifically peanut allergy—from the perspective that tolerance to foods is a normal state, just as tolerance to self-proteins is a normal state. From this vantage point, loss of tolerance to foods in food-allergic individuals can be viewed as parallel to the loss of tolerance to self-proteins in those with autoimmune diseases. Although our knowledge base is far from satisfactory, there are important similarities in the immunologic abnormalities that are characteristic of both peanut allergy and several autoimmune diseases. Delineation of these similarities may open the door to new therapeutic approaches for the treatment of severe food allergies.

Keywords Peanut allergy · Food allergy · Autoimmunity · Autoimmune diseases · Peanuts · Allergy · Thyroiditis · Myasthenia gravis · Therapy

Introduction

Hypersensitivity to foods is now recognized as a global problem in the industrialized world, and its prevalence is

increasing [1, 2]. Reactions to foods, particularly peanuts, are thought to be the most common cause of anaphylaxis occurring outside the hospital [3]. Although not all individuals who are sensitized (elevated allergen-specific IgE) are clinically allergic, much attention has been directed toward understanding how and why IgE is generated and how effector cells (mast cells and basophils) are activated [4–6]. Treatment with anti-IgE increases the threshold dose of peanut that causes a clinical reaction, although this does not cure the disease [7]. Substantial efforts are being made to desensitize patients orally and to develop other forms of treatment [8–12].

Four ideas stimulated the writing of this article. The first is the appreciation that patients with peanut allergy, who have rarely eaten peanuts and are not currently ingesting peanuts, have much higher IgG to peanut proteins than do controls who are not peanut allergic (PA) and who eat peanuts on a regular basis [13, 14, 15•]. Similarly, in some autoimmune diseases, IgG antibodies are the hallmark of disease but are also present in unaffected controls. The second idea is from a recent review by Valenta and colleagues [16], in which several links between allergy and autoimmunity are discussed. For example, IgE recognition of autoantigens may augment inflammation in diseases such as atopic dermatitis [16]. Furthermore, they reviewed evidence that the important allergen, plant profilin, has a human analog. The third concept is that research in both allergy and autoimmunity is focused on the regulation of both T cells and B cells by a variety of regulatory T cells (Tregs) [17, 18, 19••]. As an example of the possible importance of Tregs, the human disease IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome), which is caused by mutations in the *FOXP3* gene resulting in loss of CD4⁺ CD25⁺ Tregs, is characterized by a variety of autoantibodies, eosinophilia, and elevated IgE [20]. The fourth comes from considering the somewhat hackneyed but provocative

M. A. Martucci · S. C. Dreskin (✉)
Division of Allergy and Clinical Immunology, Department of
Medicine, University of Colorado Denver School of Medicine,
Campus Box B164, 12700 East 19th Avenue, Room 10002,
Aurora, CO 80045, USA
e-mail: stephen.dreskin@ucdenver.edu

M. A. Martucci
Division of Allergy and Immunology, Department of Medicine,
National Jewish Health,
Denver, CO, USA

proposal that “you are what you eat” [21]. If, indeed, we are what we eat, then foods are really an extension of our selves, and food allergy and autoimmunity may be more similar than current evidence suggests.

Based on this line of reasoning, we argue that the normal state with regard to foods is to be “tolerant” of peanut proteins and other food allergens in the same sense that the normal state for the body is to be “tolerant” of “self”-proteins (eg, thyroglobulin, thyroperoxidase, and acetylcholine receptors). In autoimmunity, losing this tolerance predisposes individuals to diseases such as Hashimoto’s thyroiditis (HT) and myasthenia gravis. Thus, although we are not implying that food allergy is an “autoimmune” disease per se, our goal is to examine the parallels between peanut allergy and autoimmunity and to explore whether these similarities could potentially be exploited for the development of novel therapies for peanut allergy in particular and food allergy in general.

Autoantibodies and Allergen-Specific Antibodies

Autoantibodies in Selected Autoimmune Diseases

The immunologic basis of autoimmune diseases has not been thoroughly elucidated, but it is generally accepted that tolerance to self occurs via a variety of immunologic mechanisms, including deletion of autoreactive lymphocytes, sequestration of autoreactive lymphocytes from sites at which self-antigen is expressed, developmental arrest, anergy, and secondary to regulatory factors such as Tregs [22, 23]. Loss of tolerance can result in damage to the organism based on activation of the T-cell or B-cell components [22, 23]. For the purposes of this discussion, we focus on the B-cell component and two autoimmune diseases characterized by the presence of IgG antibodies directed against tissue components.

A well-studied example of an autoimmune disease in which there is a distinct cutoff for the level of antibodies that are considered “normal” from the level of antibodies that are considered “abnormal” is autoimmune thyroiditis. However, there is ongoing debate as to whether those with thyroid dysfunction have antibodies that are different (eg, complement fixing) from those individuals without overt thyroid disease. HT, a form of autoimmune thyroiditis, is characterized by lymphocytic infiltration of the thyroid gland and production of IgG antibodies that recognize thyroid-specific antigens. It is currently thought that the disease is caused by abnormal suppressor T-lymphocyte function that results in a localized cell-mediated immune response directed toward the thyroid parenchymal cells [24]. Patients with HT have antibodies to various thyroid antigens, the most frequently detected of which include

antithyroid peroxidase, antithyroglobulin, and to a lesser extent thyroid-stimulating hormone receptor antibodies [25]. Importantly, patients without disease also demonstrate these antibodies, albeit at a lower level [26]. Although the differences between HT patients and those without HT are more dramatic than seen with PA versus peanut-tolerant (PT) individuals, this can be explained in part by the exclusion of those clinically euthyroid patients with autoantibodies and mildly elevated thyroid-stimulating hormone from the population of controls [26].

A second example is myasthenia gravis, which is characterized by IgG antibodies directed toward the acetylcholine receptor at the neuromuscular junction. These antibodies reduce the number of available acetylcholine receptors by causing accelerated endocytosis and degradation of the receptors, functional blockade of the acetylcholine-binding sites, and complement-mediated damage to acetylcholine receptors [27]. Lindstrom and colleagues [28] demonstrated that levels of antibody to acetylcholine receptors, although clearly higher in disease states, were present at variable levels, and these levels overlapped with those that were clearly present in some healthy controls.

Allergen-Specific Immunoglobulin Levels in Peanut Allergy

Although production of allergen-specific IgE is an absolute requirement for most allergic diseases, it has been underappreciated that allergic processes are also characterized by elevations in allergen-specific IgG in affected compared with unaffected individuals [29•]. Over the past three decades, there have been multiple reports that allergen-specific IgG (and, when measured, IgG₁ and IgG₄) tends to be higher in atopic individuals than in nonatopic individuals [29•]. This has been reported for grass (Rye 1) [30], ragweed (AgE) [31], birch (Bet v 1) [32], and peanut (crude peanut extract) [13, 14, 15•]. Elevated peanut protein-specific IgG levels in severely PA patients correlate well (Pearson $r=0.63$; $P<0.0001$) with peanut-specific IgE levels [15•]. Lesser differences were reported for cat (Fel d 1), although the allergic individuals again had higher levels [33]. No differences were reported with IgG to ovalbumin [14].

As mentioned previously, PA individuals, who do not eat peanuts, have much higher levels of peanut-specific total IgG, IgG₁, and IgG₄ than do PT individuals who eat peanuts on a regular basis [13, 14, 15•]. Of course, PA individuals likely have been exposed to small amounts of peanut proteins transplacentally, via breast milk, by inhalation, or transcutaneously, and may continue to have episodic subthreshold exposures much lower than those encountered by PT individuals. Whether these miniscule exposures lead to continued production of peanut IgG remains to be elucidated [34]. Furthermore, peanut allergy is found in infants who are born to mothers who are not

eating peanuts [6]. On the other hand, PT individuals, despite having a known frequent antigenic stimulus (as discussed above), tend to have low or undetectable levels of anti-peanut IgG. These IgG antibodies found at higher levels in PA compared with PT individuals are not likely pathogenic or protective. They are the likely result of IgG-positive B cells that naturally occur in individuals destined to class-switch to produce pathogenic IgE antibodies in the PA individuals. We are struck by the similarity to what is seen in some autoimmune diseases in which IgG antibodies are clearly higher in those with disease but still present in unaffected controls.

Immunologic Mechanisms of Peanut Allergy

The immunologic basis for peanut allergy is not fully understood, yet suggested mechanisms are in some ways similar to those proposed for autoimmunity. For example, proliferative responses of isolated lymphocytes to peanut proteins are similar in PA individuals compared with PT and peanut-sensitized individuals and nonallergic controls [35–37]. However, primary T-cell lines derived from PA individuals exhibit greater proliferative responses to purified allergens than do similar lines derived from peanut-sensitized patients [37]. It is attractive to consider a role for CD25⁺ forkhead box P3⁺ Tregs in naturally occurring peanut allergy and in induced tolerance to peanuts, but the published evidence to support this idea is weak [12, 38, 39]. Finally, it is possible that food allergy is caused at least in part by a loss of mucosal tolerance due to abnormal gut permeability. However, the nature of this abnormal gut-specific immune function based on permeability is not well-defined and cannot explain antigen specificity seen in PA individuals [40].

To summarize this section, peanut-specific IgG is present in PT individuals and elevated in PA individuals in the same way that antithyroglobulin and antithyroid peroxidase antibodies and anti-acetylcholine antibodies are present in healthy individuals, yet elevated in those with HT and myasthenia

gravis. We argue that although the IgG in PA individuals is not pathogenic, it is generated as part of the natural development of IgE-positive B cells and IgE-secreting plasma cells that are essential for clinically important peanut allergy. Therefore, allergen-specific IgG is a biomarker for pathogenic IgE. Table 1 outlines some of the similarities and differences between peanut allergy and selected autoimmune diseases.

Are Immunomodulatory Approaches that are Useful for Autoimmune Diseases Applicable to the Treatment of Peanut Allergy and Possibly Other Severe Food Allergies?

Pathogenic IgE is produced by IgE-producing plasma cells. Targeting of these cells is likely to have an impact on allergic diseases, and peanut allergy in particular. Rituximab is a chimeric murine antihuman CD20 monoclonal antibody initially developed for the treatment of follicular lymphoma. It targets CD20 and mediates B-cell depletion, including direct B-cell apoptosis, complement-mediated cytotoxicity, and antibody-dependent cell-mediated killing [41].

Rituximab has been used with good success in several autoimmune diseases, including rheumatoid arthritis, immune (idiopathic) thrombocytopenic purpura, autoimmune hemolytic anemia, and systemic lupus erythematosus. Two separate groups have observed preferential effects on memory B cells and a significant decrease in rheumatoid factor levels over several months [42, 43]. Zaja and colleagues [44] showed that immune (idiopathic) thrombocytopenic purpura patients treated with rituximab had a 62% complete response rate with elimination of antiplatelet IgG for more than 6 months. Penalver et al. [45] demonstrated that patients with autoimmune hemolytic anemia treated with rituximab had a 77% response rate with complete elimination of anti-red blood cell IgG for more than 6 months. Arguing against the use of this drug is its lack of effect on IgE levels in atopic dermatitis even though there was clinical efficacy [46]. It is important to note that although plasma cells are derived from B cells,

Table 1 Similarities and differences between peanut allergy and autoimmune disease

	Peanut allergy	Autoimmune disease
Prevalence	Increasing	Increasing
IgE antibodies to offending antigens are present and pathogenic	Yes	No
IgG antibodies to offending antigens are present in disease	Yes	Yes
IgG antibodies to offending antigens are pathogenic	No ^a	Yes
Loss of natural tolerance	Arguable	Yes
Loss of regulatory T-cell function	Some evidence	Yes
T-helper type 2-mediated response	Yes	No
T-helper type 1 immune response	Yes	Yes
Response to immunomodulatory drugs	Unknown	Yes

^a In some cases, they may have protective activity

plasma cells are long-lived, do not express CD20, and are not targets of rituximab [47]. From this point of view, it is remarkable that rituximab has as much effect as it does on IgG levels, and likely exerts its effects via other mechanisms. It has been postulated that rituximab is effective because it removes the precursors of plasma cells producing pathogenic autoantibody species, depletes a critical mass of autoreactive B-cell clones that present antigen to pathogenic autoreactive T cells, or eliminates an important source of cytokines and chemokines [48]. Although the ultimate mechanism is not known, rituximab provides a means to disrupt and alter these pathologic B cells in several autoimmune diseases.

Therapies directed against activated B cells or plasma cells are at various stages of development [49••]. Three specific targets are attracting current attention, BAFF (B-lymphocyte activation factor), APRIL (a proliferation-inducing ligand), and the ubiquitin proteasome [49••]. BAFF and APRIL have a central role in B-cell development. BAFF is essential to the survival of late-transitional, naïve, and marginal zone B cells but does not influence the survival of memory cells [49••]. In contrast, APRIL is important to the survival of short-lived and long-lived plasma cells. The viability of plasma cells is severely compromised by combined blockade of BAFF and APRIL [49••, 50]. BAFF levels also regulate early autoreactive B cells, and this regulation by excess BAFF is likely to play a major role in the generation of B-cell autoimmunity in several autoimmune diseases. Anti-BAFF antibodies (eg, belimumab) provide selective BAFF blockade, whereas blocking both BAFF- and APRIL-mediated signaling disrupts the entire signaling cascade. Belimumab is now US Food and Drug Administration approved for treatment of systemic lupus erythematosus and has shown clinical promise and safety in patients with rheumatoid arthritis [51, 52]. Drugs that directly attack plasma cells are recent developments. The proteasome inhibitor bortezomib is a selective inhibitor of the ubiquitin proteasome that is very active in plasma cells, and can lead to cell cycle arrest and apoptosis [49••]. In addition, proteasome inhibitors block nuclear factor- κ B and can inhibit activated B cells and dendritic cells [49••, 53]. These therapies provide promise in the treatment of several autoimmune diseases and may provide additional tools for future therapies for patients with severe food allergies.

Conclusions

In conclusion, we believe that peanut allergy specifically, and perhaps other allergies as well, has a great deal in common with selected autoimmune diseases. Although current therapies directed against B-lineage cells are not

particularly effective in significantly altering levels of pathologic antibody in autoimmune diseases, plasma cell-directed therapies may become better targeted and clinically more viable in the future. Thus, it is reasonable to expect that there will eventually be a role for B-cell-targeted therapies used alone or in concert with other approaches for the treatment of severe, life-threatening food allergy.

Acknowledgment This work was supported by National Institutes of Health grant RO1-AI052164 (to Dr. Dreskin).

Disclosure Dr. Martucci and Dr. Dreskin have served on the American Board of Allergy and Immunology.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic. *J Allergy Clin Immunol.* 2007;120(3):491–503. quiz 4–5.
2. Ben-Shoshan M, Kagan RS, Alizadehfar R, Joseph L, Turnbull E, St Pierre Y, et al. Is the prevalence of peanut allergy increasing? A 5-year follow-up study in children in Montreal. *J Allergy Clin Immunol.* 2009;123(4):783–8.
3. Burks AW. Peanut allergy. *Lancet.* 2008;371(9623):1538–46.
4. Hourihane JO, Warner JO. Allergy to peanut. *Lancet.* 1996;348(9040):1523.
5. Sicherer SH, Sampson HA. Food allergy: recent advances in pathophysiology and treatment. *Annu Rev Med.* 2009;60:261–77.
6. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol.* 2010;125(2 Suppl 2):S116–25.
7. Leung D, Sampson H, Yunginger J, Burks A, Schneider L, Wortel C, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med.* 2003;348(11):986–93.
8. Burks W, Sampson HA, Bannon GA. Peanut allergens. *Allergy.* 1998;53(8):725–30.
9. Wang J, Sicherer SH. Immunologic therapeutic approaches in the management of food allergy. *Expert Rev Clin Immunol.* 2009;5(3):301–10.
10. Li XM. Traditional Chinese herbal remedies for asthma and food allergy. *J Allergy Clin Immunol.* 2007;120(1):25–31.
11. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol.* 2009;124(2):286–91. 91 e1–6.
12. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol.* 2009;124(2):292–300. e1–97.
13. Kolopp-Sarda MN, Moneret-Vautrin DA, Gobert B, Kanny G, Guerin L, Faure GC, et al. Polyisotypic anti-peanut-specific humoral responses in peanut-allergic individuals. *Clin Exp Allergy.* 2001;31(1):47–53.
14. Tay SS, Clark AT, Deighton J, King Y, Ewan PW. Patterns of immunoglobulin G responses to egg and peanut allergens are

- distinct: ovalbumin-specific immunoglobulin responses are ubiquitous, but peanut-specific immunoglobulin responses are up-regulated in peanut allergy. *Clin Exp Allergy*. 2007;37(10):1512–8.
15. • Dreskin SC, Tripputi MT, Aubrey MT, Mustafa SS, Atkins D, Leo HL, et al. Peanut-allergic subjects and their peanut-tolerant siblings have large differences in peanut-specific IgG that are independent of HLA class II. *Clin Immunol*. 2010;137(3):366–73. *This article demonstrates that IgG directed against peanut proteins is elevated in patients with peanut allergy, that PT individuals have lower but usually measurable amounts of this IgG, and that these findings are independent of HLA class II.*
 16. Valenta R, Mittermann I, Werfel T, Garn H, Renz H. Linking allergy to autoimmune disease. *Trends Immunol*. 2009;30(3):109–16.
 17. Basten A, Fazekas de St Groth B. Special regulatory T-cell review: T-cell dependent suppression revisited. *Immunology*. 2008;123(1):33–9.
 18. Sakaguchi S, Miyara M, Costantino CM, Hafler DA. FOXP3+ regulatory T cells in the human immune system. *Nat Rev Immunol*. 2010;10(7):490–500.
 19. • Curotto de Lafaille MA, Lafaille JJ, Graca L. Mechanisms of tolerance and allergic sensitization in the airways and the lungs. *Curr Opin Immunol*. 2010;22(5):616–22. *This is an excellent review of mechanisms of regulation likely to be at play in tolerance to allergens.*
 20. Arason GJ, Jorgensen GH, Ludviksson BR. Primary immunodeficiency and autoimmunity: lessons from human diseases. *Scand J Immunol*. 2010;71(5):317–28.
 21. Brillat-Savarin A. Physiologie du Gout, ou Meditations de Gastronomie Transcendante 1826.
 22. Strasser A, Puthalakath H, O'Reilly LA, Bouillet P. What do we know about the mechanisms of elimination of autoreactive T and B cells and what challenges remain. *Immunol Cell Biol*. 2008;86(1):57–66.
 23. Anderson MS, Su MA. Aire and T cell development. *Curr Opin Immunol*. 2010 (Epub ahead of print).
 24. Hadj-Kacem H, Rebuffat S, Mnif-Feki M, Belguith-Maalej S, Ayadi H, Peraldi-Roux S. Autoimmune thyroid diseases: genetic susceptibility of thyroid-specific genes and thyroid autoantigens contributions. *Int J Immunogenet*. 2009;36(2):85–96.
 25. Tagami T, Tamanaha T, Shimazu S, Honda K, Nanba K, Nomura H, et al. Lipid profiles in the untreated patients with Hashimoto thyroiditis and the effects of thyroxine treatment on subclinical hypothyroidism with Hashimoto thyroiditis. *Endocr J*. 2010;57(3):253–8.
 26. Smith BR, Bolton J, Young S, Collyer A, Weeden A, Bradbury J, et al. A new assay for thyrotropin receptor autoantibodies. *Thyroid*. 2004;14(10):830–5.
 27. Drachman DB. Myasthenia gravis. *N Engl J Med*. 1994;330(25):1797–810.
 28. Lindstrom JM, Seybold ME, Lennon VA, Whittingham S, Duane DD. Antibody to acetylcholine receptor in myasthenia gravis. Prevalence, clinical correlates, and diagnostic value. *Neurology*. 1976;26(11):1054–9.
 29. • Thomas WR, Hales BJ. Immune responses to inhalant allergens. *WAO Journal*. 2008:89–95. *This is an excellent review of mechanisms thought to play a role in tolerance to inhaled allergens*
 30. Platts-Mills TA. Local production of IgG, IgA and IgE antibodies in grass pollen hay fever. *J Immunol*. 1979;122(6):2218–25.
 31. Platts-Mills TA, von Maur RK, Ishizaka K, Norman PS, Lichtenstein LM. IgA and IgG anti-ragweed antibodies in nasal secretions. Quantitative measurements of antibodies and correlation with inhibition of histamine release. *J Clin Invest*. 1976;57(4):1041–50.
 32. Benson M, Reinholdt J, Cardell LO. Allergen-reactive antibodies are found in nasal fluids from patients with birch pollen-induced intermittent allergic rhinitis, but not in healthy controls. *Allergy*. 2003;58(5):386–92.
 33. Jarvis D, Zock JP, Heinrich J, Svanes C, Verlato G, Olivieri M, et al. Cat and dust mite allergen levels, specific IgG and IgG4, and respiratory symptoms in adults. *J Allergy Clin Immunol*. 2007;119(3):697–704.
 34. Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. *N Engl J Med*. 2003;348(11):977–85.
 35. Thottungal TB, Stefura BP, Simons FE, Bannon GA, Burks W, HayGlass KT. Human subjects without peanut allergy demonstrate T cell-dependent, TH2-biased, peanut-specific cytokine and chemokine responses independent of TH1 expression. *J Allergy Clin Immunol*. 2006;118(4):905–14.
 36. Turcanu V, Winterbotham M, Kelleher P, Lack G. Peanut-specific B and T cell responses are correlated in peanut-allergic but not in non-allergic individuals. *Clin Exp Allergy*. 2008;38(7):1132–9.
 37. Flinterman AE, Pasmans SG, den Hartog Jager CF, Hoekstra MO, Bruijnzeel-Koomen CA, Knol EF, et al. T cell responses to major peanut allergens in children with and without peanut allergy. *Clin Exp Allergy*. 2010;40(4):590–7.
 38. van Wijk F, Wehrens EJ, Nierkens S, Boon L, Kasran A, Pieters R, et al. CD4+CD25+ T cells regulate the intensity of hypersensitivity responses to peanut, but are not decisive in the induction of oral sensitization. *Clin Exp Allergy*. 2007;37(4):572–81.
 39. Skrinde I, Farkas L, Kvale EO, Johansen FE, Jahnsen FL. Depletion of CD4(+)CD25(+)CD127(lo) regulatory T cells does not increase allergen-driven T cell activation. *Clin Exp Allergy*. 2008;38:1752–9.
 40. Vighi G, Marcucci F, Sensi L, Di Cara G, Frati F. Allergy and the gastrointestinal system. *Clin Exp Immunol*. 2008;153 Suppl 1:3–6.
 41. Taylor RP, Lindorfer MA. Drug insight: the mechanism of action of rituximab in autoimmune disease—the immune complex decoy hypothesis. *Nat Clin Pract Rheumatol*. 2007;3(2):86–95.
 42. Nakou M, Katsikas G, Sidiropoulos P, Bertsias G, Papadimitraki E, Raptopoulou A, et al. Rituximab therapy reduces activated B cells in both the peripheral blood and bone marrow of patients with rheumatoid arthritis: depletion of memory B cells correlates with clinical response. *Arthritis Res Ther*. 2009;11(4):R131.
 43. Cambridge G, Leandro MJ, Teodorescu M, Manson J, Rahman A, Isenberg DA, et al. B cell depletion therapy in systemic lupus erythematosus: effect on autoantibody and antimicrobial antibody profiles. *Arthritis Rheum*. 2006;54(11):3612–22.
 44. Zaja F, Vianelli N, Volpetti S, Battista ML, Defina M, Palmieri S, et al. Low-dose rituximab in adult patients with primary immune thrombocytopenia. *Eur J Haematol*. 2010;85(4):329–34.
 45. Penalver FJ, Alvarez-Larran A, Diez-Martin JL, Gallur L, Jarque I, Caballero D, et al. Rituximab is an effective and safe therapeutic alternative in adults with refractory and severe autoimmune hemolytic anemia. *Ann Hematol*. 2010;89(11):1073–80.
 46. Simon D, Hosli S, Kostylina G, Yawalkar N, Simon HU. Anti-CD20 (rituximab) treatment improves atopic eczema. *J Allergy Clin Immunol*. 2008;121(1):122–8.
 47. Oracki SA, Walker JA, Hibbs ML, Corcoran LM, Tarlinton DM. Plasma cell development and survival. *Immunol Rev*. 2010;237(1):140–59.
 48. Leandro MJ, de la Torre I. Translational mini-review series on B cell-directed therapies: the pathogenic role of B cells in autoantibody-associated autoimmune diseases—lessons from

- B cell-depletion therapy. Clin Exp Immunol. 2009;157(2):191–7.
49. •• Calero I, Nieto JA, Sanz I. B cell therapies for rheumatoid arthritis: beyond B cell depletion. Rheum Dis Clin North Am. 2010;36(2):325–43. *This review discusses the limitations of current therapies directed toward depletion of B cells and outlines evolving therapies that target plasma cells.*
 50. Moisini I, Davidson A. BAFF: a local and systemic target in autoimmune diseases. Clin Exp Immunol. 2009;158(2):155–63.
 51. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM241199.pdf>. Summary Minutes of the Arthritis Advisory Committee Meeting November 16, 2010. U.S. Food and Drug Administration (FDA).
 52. Tak PP, Thurlings RM, Rossier C, Nestorov I, Dimic A, Mircetic V, et al. Atacicept in patients with rheumatoid arthritis: results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating, single- and repeated-dose study. Arthritis Rheum. 2008;58(1):61–72.
 53. van der Heijden JW, Oerlemans R, Lems WF, Scheper RJ, Dijkmans BA, Jansen G. The proteasome inhibitor bortezomib inhibits the release of NFkappaB-inducible cytokines and induces apoptosis of activated T cells from rheumatoid arthritis patients. Clin Exp Rheumatol. 2009;27(1):92–8.