Clinic Rev Allerg Immunol (2007) 33:199–203
DOI 10.1007/s12016-007-0043-6

Emerging Treatment of Atopic Dermatitis

Chih-Jung Hsu · Li-Fang Wang

Published online: 13 July 2007

Abstract Atopic dermatitis is a chronically relapsing eczematous disease of the skin. A wide range of therapeutic regimens has been used for atopic dermatitis. A better understanding of its pathogenesis will also lead to the development of novel approaches to treating this disease. This article reviews the recent advances in allergen-specific sublingual immunotherapy and therapy with antileukotriene drugs, probiotics, mycophenolate mofetil, leflunomide, and intermittent fluticasone propionate ointment, which the authors expect will be clinically useful therapies in the near future.

Keywords Atopic dermatitis · Sublingual immunotherapy · Probiotic · Leukotriene antagonists · Mycophenolate mofetil · Leflunomide · Fluticasone propionate

Abbreviations

AD	Atopic dermatitis
LTs	Leukotrienes
MMF	Mycophenolate mofetil
SLIT	Allergen-specific sublingual immunotherapy
FP	Fluticasone propionate

Introduction

Atopic dermatitis (AD) is a chronically relapsing eczematous disease that occurs in persons of all ages but is more common in children. AD has been reported to affect more than 10% of children in most countries [1]. The disease is characterized by intense pruritus and a course marked by exacerbation and remissions. The pathogenesis of AD is complex and mostly obscure, involving epidermal barrier defect, genetic predisposition, and immunological dysfunction [2]. Although skin hydration, irritant avoidance, antihistamine, topical corticosteroids, phototherapy, and immunosuppressive agents are the mainstays of therapy, AD is usually poorly responsive or refractory to them. Thus, new therapies with good efficacy, safety, and tolerability are continually being sought. This review article is not intended to be a comprehensive survey of the reported literature about new AD treatments. Nevertheless, among the clinical trials presented, some are not double-blind, randomized in design and, therefore, are of less scientific merit. Our purpose is to select those emerging strategies that we expect will help AD patients in the near future.

Leukotriene Antagonists

The leukotrienes (LTs) are products of the arachidonic acid metabolism by way of the 5-lipoxygenase pathway. LTs are divided into two groups according to their chemical structure: those that have a sulfur linkage (cysteinyl LTs: LTC_4, LTD_4 LTE_4), and those that do not (LTB_4) [3]. Eosinophils, basophils, and mast cells are the most important sources of LTs. It has long been known that cysteinyl LTs contribute to airway smooth muscle constriction, eosinophil migration, vascular permeability, and edema in the pathogenesis of asthma [4]. Thus, research programs aimed to identify substances that could inhibit the action or synthesis of LTs have been ongoing since the 1980s. In the late 1990s, three chemically distinct cysteinyl LT-receptor antagonists (montelukast, pranlukast, and zafir-

C.-J. Hsu · L.-F. Wang (✉)
Department of Dermatology,
National Taiwan University Hospital,
Taipei, Taiwan, Republic of China
e-mail: lifangwa@ha.mc.ntu.edu.tw

lukast) became available for the treatment of asthma [5]. Many studies have demonstrated the efficacy and tolerability of these novel drugs as therapeutic agents for asthma. There are two rationales for using these drugs to treat AD. First, their use for asthma has led to the observation of favorable outcomes in cases with concomitant AD. Second, LTs have been implicated in the pathogenesis of AD [6]. In 1998, one pilot study from the US reported that the LT antagonist zafirlukast successfully alleviated symptoms of AD [7]. Thereafter, four groups from the US, Italy, and Hong Kong reported that montelukast is an effective adjuvant treatment for AD [8–11]. Recently, Hon et al. reported that montelukast at doses recommended for asthma treatment reduces disease severity and increases soluble CD14 levels in children with AD [12]. Another inhibitor of LT synthesis, zileuton blocks both cysteinyl LTs and LTB_4 (the latter directing T cell migration and recruitment to allergic sites [13]). Woodmansee and Simon published the only report to describe the effect of zileuton in AD. In their pilot study, zileuton significantly improved the symptoms and objective skin findings seen in AD [14]. Although most studies showed favorable effects of LT antagonists in AD, the study of Silverberg and Paller found that LT receptor antagonists are ineffective for severe AD [15]. Thus, more trials and studies are needed to determine the role of LTs in the pathogenesis of AD and to confirm the efficacy and tolerability of LT receptor inhibitors, as well as to determine the optimal timing and dosing for their treatment of AD.

Probiotics

The "hygiene hypothesis" proposed by Strachan suggested that the increase in prevalence of atopic disease noted in the last several decades is related to reduced exposure to microbes [16]. Immune responses in neonates are dominated by Th2 cytokines and require the stimulation from various microorganisms in the environment to shift to Th1-based immune responses. One important source of stimulation is gastrointestinal microflora. The gastrointestinal tract of the newborn is sterile at birth, but throughout the first year of life, it is colonized by many microorganisms. These resident microflora are involved in the activation of innate and adaptive immunity. Their essential roles in the development of appropriate immunity were repeatedly demonstrated by studies in germ-free animals, which have diminished intestinal lymphocytes and poor immunoglobulin diversity [17]. Thus, several studies have hypothesized and confirmed that allergic disease in children may be associated with differences in their intestinal microflora. Bjorksten's study showed that allergic children were less often colonized with lactobacilli and harbored higher counts of coliforms and *Staphylococcus aureus* [18]. Kirjavainen et al. assessed the fecal microflora of healthy infants and infants with AD during breast-feeding and after weaning and showed that atopic infants had lower counts of Gram-positive species and bifidobacteria and higher counts of bacteroides [19]. Kalliomäki et al., via analysis of the bacterial cellular fatty acid profile of stool samples, demonstrated that difference in neonatal gut microflora precedes development of atopy [20].

Probiotics are microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being of the host. Lactic acid bacteria, in particular specific lactobacilli and bifidobacterium species, are widely used because they can resist gastric acid and enzymes, adhere to colonic mucosa, and colonize the intestinal tract easily. Although the exact mechanism of action of probiotics is still unknown and nowadays under intensive investigation, probiotics are believed to restore intestinal permeability, microecology, and immunological barrier function, and to downregulate proinflammatory cytokines [21]. In clinical trials to date, probiotics appear to be useful for the treatment of AD and even in primary prevention of atopy. In 1997, Majamaa et al. from Finland reported that the clinical score of AD improved significantly during the 1-month study period in infants treated with extensively hydrolyzed whey formula fortified with *Lactobacillus* GG, but not in those treated with the same formula without *Lactobacillus* GG [22]. In 2000, Isolauri et al. reported a similar favorable result when probiotic-supplemented formulas were given to infants for 2 months [23]. In 2003, a group from Denmark reported a double-blind, placebo-controlled, crossover study of probiotics given to 1- to 13-year-old children with AD for 6 weeks. After active treatment, more patients experienced improvement of their eczema in the probiotic group than in the placebo group, although the total SCORAD index did not change significantly [24]. Very recently, Weston's study showed that supplementation with probiotics is beneficial in improving the extent and severity of AD in young children with moderate or severe disease [25]. By contrast, Viljanen reported no difference between the probiotics group (given probiotics concomitant with elimination diet and skin treatment) and placebo group [26] of a randomized double-blind study in infants with suspected cow's milk allergy (CMA). Most importantly, Kalliomäki assessed the effect of probiotics on atopic disease by giving *Lactobacillus* GG parenterally to mothers (who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma) and to their infants postnatally for 6 months. Follow-up of these children at the ages of 2 and 4 years both showed that the frequency of atopic eczema in the probiotic group was only half that of the placebo group [27, 28]. Hence, probiotics are effective in preventing early atopic disease in children at high risk, and the preventive

effect extends beyond infancy. With regard to cytokine profiles after probiotic treatment, data are limited and conflicting. Pessi et al. reported that serum IL-10 level was elevated after treatment, whereas serum IL-6, IL-12, IFN-γ, and TNF-α levels were low and remained comparable throughout the study period [29]. In contrast, Pohjavuori et al. reported that secretion of IFN-γ by peripheral blood mononuclear cells before the treatment was significantly lower in infants with CMA than in non-CMA infants. Among the infants who received probiotic, the level of secreted IFN-γ increased when compared with the placebo group [30]. Collectively, evidence supports that probiotics may be an important complementary approach in the treatment and prevention of AD.

Allergen-Specific Sublingual Immunotherapy

Allergen-specific immunotherapy is the practice of administering increasing amounts of allergens to allergic individuals to hyposensitize and reduce the symptoms stemming from natural exposure to the allergen. Although subcutaneous immunotherapy (SCIT) is common, other routes of administration (oral, nasal, sublingual, or bronchial routes) have been evaluated [31]. The nasal and bronchial routes have been gradually abandoned because of local side effects, and the oral route is less favored because the dose required is large and more likely to induce gastrointestinal side effects [32]. In contrast, allergen-specific sublingual immunotherapy (SLIT) was proven to be an effective treatment for respiratory allergy in a great number of trials [33]. Therefore, SLIT is presently the most widely used noninjection immunotherapy in Europe. Two important points are worth noting. The first is that SLIT (unlike SCIT) has an extremely satisfactory tolerability and safety [34, 35]. The second is that its effect is long-lasting, as demonstrated recently by Rienzo et al. [36]. There are only a few reports of SLIT of AD. In the 1990s, there were two studies [37]. One showed significant skin lesion improvement in 64.4% of SLIT-treated patients with moderate-to-severe AD, and the other showed significant reduction in total IgE levels and symptoms in children with AD treated 2 years with SLIT. In 2000, Mastrandrea et al. reported that 3 years of SLIT resulted in complete disappearance of skin lesions at 6-year follow-up in 70% of 35 consecutive patients with mild to moderate AD [38]. In 2003, Bordignon et al. reported a decrease in skin reactivity after SLIT [39]. Double-blind, well-controlled studies will be required before SLIT can be accepted as a standard treatment of AD. However, because it is safe and potentially able to induce mucosal immunity to interfere with the systemic aspects of allergic inflammation, SLIT is regarded as a candidate treatment for AD.

Mycophenolate Mofetil and Leflunomide

Immunosuppressive agents, including glucocorticoid, azathioprine, and cyclosporine, are effective to treat severe AD. However, their usage is usually limited by a wide range of severe side effects [40]. Thus, new immunosuppressive agents with an improved risk–benefit ratio are of great interest. Among them, mycophenolate mofetil (MMF) and leflunomide have attracted the most attention. MMF inhibits the enzyme inosine monophosphatase dehydrogenase (IMPDH), which is a key enzyme in de novo purine biosynthesis. Moreover, MMF is a fivefold more potent inhibitor of the type II isoform of IMPDH, which is expressed in activated B and T cells, than of the type I isoform, which is expressed in most mammalian cells. Therefore, MMF function is a specific inhibitor of T and B lymphocyte activation and proliferation [41]. Several studies have examined the efficacy of MMF in the treatment of AD. In 1999, Grundmann-Kollmann et al. first reported successful treatment of severe refractory AD with a 2-month course of MMF [42]. The next year they reported that MMF was effective in 10 consecutive patients with moderate-to-severe AD nonresponsive to standard therapy [43]. No relapse of the disease was noted 20 weeks after the cessation of treatment. Then, Neuber et al. and Benez and Fierlbeck reported similar favorable results [44, 45]. However, Hansen et al. reported a negative result and Satchell and Barnetson reported that staphylococcal septicemia and endocarditic complicated the MMF treatment of AD [46, 47].

Leflunomide inhibits the de novo synthesis of pyrimidine. Unlike other cells, activated lymphocytes expand their pyrimidine pool approximately eightfold during proliferation. To meet this demand, lymphocytes must use both salvage and de novo synthesis pathways, and as a result, leflunomide inhibits autoimmune T-cell proliferation and B-cell antibody production. In contrast, other cells can maintain their basal homeostasis and meet cell division requirements for pyrimidine nucleotides through the use of salvage pathways for pyrimidine synthesis. Thus, other cells are not subject to leflunomide inhibition [41]. In 1999, one study showed that leflunomide inhibits murine IgE and immediate cutaneous hypersensitivity responses to ovalbumin [48]. Till now, only one clinical report has evaluated the efficacy of leflunomide as long-term treatment of AD. They treated two patients with severe AD for 20 months with leflunomide and observed a significant improvement [49]. In summary, compared with most systemic immunosuppressive agents, MMF and leflunomide seem to have more favorable risk–benefit ratios. These agents may prove to be especially beneficial for patients with hypertension, impaired renal function, or liver diseases that rule out the use of other immunotherapies.

Intermittent Maintenance Treatment with Fluticasone Propionate

Whereas the efficacy and safety of topical corticosteroids in the treatment of active AD is well-documented, their use as maintenance treatment, which seeks to control symptoms without incurring side-effects, is just emerging. Compared with corticosteroids of similar potency, fluticasone propionate (FP) ointment is as effective in treating the acute symptoms of AD but has a more favorable safety profile. In 1999, Van Der Meer et al. reported that long-term treatment with FP ointment applied once daily, two times per week for 16 weeks to known healed lesions resulted in significant improvement of moderate-to-severe AD [50]. Later, Hanifin et al. reported that the risk of relapse of AD can be significantly reduced by extended intermittent dosing with FP cream [51]. Berth-Jones et al. did a randomized, double-blind, parallel group study and got similar favorable results [52]. Kirkup et al. performed a study in 2- to 14-year-old children with moderate-to-severe AD, comparing FP with hydrocortisone 1% cream and hydrocortisone butyrate 0.1% cream, and got significantly better results in the FP group in both the acute and maintenance phases [53]. Because topical steroid has been shown to be an effective treatment for autoimmune bullous disease and its effect on regulatory T cells is important in allergy, topical steroid is expected to have a role in maintenance treatment of AD [54, 55].

Conclusions

Significant gains have been made in our understanding of AD, including discovery of factors controlling recruitment of effector T cells, the role of cytokines and chemokines, and the role of infection and regulatory genes. These discoveries will continuously provide new targets for AD prevention and treatment.

References

1. Williams H, Robertson C, Stewart A, Aït-Khaled N, Anabwani G, Anderson R et al. (1999) Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. J Allergy Clin Immunol 103:125–138
2. Kang K, Stevens SR (2003) Pathophysiology of atopic dermatitis. Clin Dermatol 21:116–121
3. Norel X, Brink C (2004) The quest for new cysteinyl-leukotriene and lipoxin receptors: recent clues. Pharmacol Ther 103:81–94
4. Bochner BS, Busse WW (2005) Allergy and asthma. J Allergy Clin Immunol 115:953–959
5. Drazen JM, Israel E, O'Byrne PM (1999) Treatment of asthma with drugs modifying the leukotriene pathway. N Engl J Med 340 (3):197–206
6. Hishinuma T, Suzuki N, Aiba S, Tagami H, Mizugaki M (2001) Increased urinary leukotriene E4 excretion in patients with atopic dermatitis. Br J Dermatol 144:19–23
7. Carucci JA, Washenik K, Weinstein A, Shupack J, Cohen DE (1998) The Leukotriene antagonist zafirluksat as a therapeutic agent for atopic dermatitis. Arch Dermatol 134:785–786
8. Yanase DJ, David-Bajar CK (2001) The leukotriene antagonist montelukast as a therapeutic agent for atopic dermatitis. J Am Acad Dermatol 44:89–93
9. Capella GL, Grigerio E, Altomare G (2001) A randomized trial of leukotriene receptor antagonist montelukast in moderate-to-severe atopic dermatitis of adults. Eur J Dermatol 11(3):209–213
10. Pei AYS, Chan HHL, Leung TF (2001) Montelukast in the treatment of children with moderate-to-severe atopic dermatitis: a pilot study. Pediatr Allergy Immunol 12:154–158
11. Eustachio N, Alessandro P, Margherita F, Antonio F, Tursi A (2002) Efficacy and tolerability of montelukast as a therapeutic agent for severe atopic dermatitis in adults. Acta Derm Venereol 82:297–298
12. Hon KL, Leung TF, Ma KC, Wong Y, Fok TF (2005) Brief case series: montelukast, at doses recommended for asthma treatment, reduces disease severity and increases soluble CD14 in children with atopic dermatitis. J Dermatolog Treat 16(1):15–18
13. Luster AD, Tager AM (2004) T-cell trafficking in asthma: lipid mediators grease the way. Nat Rev Immunol 4:711–724
14. Woodmansee DP, Simon RA (1999) A pilot study examining the role of zileuton in atopic dermatitis. Ann Allergy Asthma Immunol 83(6 Pt. 1):548–552
15. Silverberg NB, Paller AS (2004) Leukotriene receptor antagonists are ineffective for severe atopic dermatitis. J Am Acad Dermatol 50:485–486
16. Strachan DP (1989) Hay fever, hygiene, and household size. Br Med J 299:1259–1260
17. Tlaskalová-Hogenová H, Štěpánková R, Hudcovic T, Tučková L, Cukrowska B, Lodinová-Žádníková R et al. (2004) Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. Immunol Lett 93:97–108
18. Björkstén B, Naaber P, Sepp E, Mikelsaar M (1999) The intestinal microflora in allergic Estonian and Swedish 2-year-old children. Clin Exp Allergy 29:342–346
19. Kirjavainen PV, Apostolou E, Arvola T, Salminen SJ, Gibson GR, Isolauri E (2001) Characterizing the composition of intestinal microflora as a prospective treatment target in infant allergic disease. FEMS Immunol Med Microbiol 32:1–7
20. Kalliomäki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E (2001) Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol 107:129–134
21. Ogden NS, Bielory L (2005) Probiotics: a complementary approach in the treatment and prevention of pediatric atopic disease. Curr Opin Allergy Clin Immunol 5:179–184
22. Majamaa H, Isolauri E (1997) Probiotics: a novel approach in the management of food allergy. J Allergy Clin Immunol 99:179–185
23. Isolauri E, Arvola T, Sütas Y, Moilanen E, Salminen S (2000) Probiotics in the management of atopic eczema. Clin Exp Allergy 30:1604–1610
24. Rosenfeldt V, Benfeldt E, Nielsen SD, Michaelsen DKF, Jeppesen DDL, Valerius NH, Paerregaard A (2003) Effect of probiotic Lactobacillus strains in children with atopic dermatitis. J Allergy Clin Immunol 111:389–395
25. Weaton S, Halbert A, Richmond P, Prescott SL (2005) Effects of probiotics on atopic dermatitis: a randomized controlled trial. http://adc.bmjjournals.com/cgi/rapidpdf/adc.2004.060673v3
26. Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T et al. (2005) Probiotics in the treatment of

atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. Allergy 60:494–500
27. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E (2001) Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial. Lancet 357:1076–1079
28. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E (2003) Probiotics and prevention of atopic disease: 4-year follow-up of a randomized placebo-controlled trial. Lancet 361:1869–1871
29. Pessi T, Sütas Y, Hurme M, Isolauri E (2000) Interleukin-10 generation in atopic children following oral Lactobacillus rhamnosus GG. Clin Exp Allergy 30:1804–1808
30. Pohjavuori E, Viljanen M, Korpela R, Kuitunen M, Tiittanen M, Vaarala O et al. (2004) Lactobacillus GG effect in increasing IFN-γ production in infants with cow's milk allergy. J Allergy Clin Immunol 114:131–136
31. Canonica GW, Passalacqua G (2003) Noninjection routes for immunotherapy. J Allergy Clin Immunol 111:437–448
32. Norman PS (2004) Immunotherapy: 1999–2004. J Allergy Clin Immunol 113:1013–1023
33. Frew AJ, Smith HE (2001) Sublingual immunotherapy. J Allergy Clin Immunol 107:441–444
34. Lombardi C, Gargioni S, Melchiorre A, Tiri A, Falagiani P, Canonica GW et al. (2001) Safety of sublingual immunotherapy with monomeric allergoid in adults: multicenter post-marketing surveillance study. Allergy 56:989–992
35. André C, Vatrinet C, Galvain S, Carat F, Sicard H (2000) Safety of sublingual-swallow immunotherapy in children and adults. Int Arch Allergy Immunol 121:229–234
36. Rienzo VD, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L et al. (2003) Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. Clin Exp Allergy 33:206–210
37. Mastrandrea F (2004) The potential role of allergen-specific sublingual immunotherapy in atopic dermatitis. Am J Clin Dermatol 5(5):281–294
38. Mastrandrea F, Serio G, Minelli M, Minardi A, Scarcia G, Coradduzza G (2000) Specific sublingual immunotherapy in atopic dermatitis. Results of 6-year follow-up of 35 consecutive patients. Allergol Immunopathol (Madr) 28:54–62
39. Bordignon V, Parmiani S (2003) Variation of the skin end-point in patients treated with sublingual specific immunotherapy. J Investig Allergol Clin Immunol 13(3):170–176
40. Akhavan A, Rudikoff D (2003) The treatment of atopic dermatitis with systemic immunosuppressive agents. Clin Dermatol 21:225–240
41. Frieling U, Luger TA (2002) Mycophenolate mofetil and leflunomide: promising compounds for the treatment of skin diseases. Clin Exp Dermatol 27:562–570
42. Grundmann-Kollmann K, Behrens L, Krähn K et al. (1999) Successful treatment of severe refractory atopic dermatitis with mycophenolate mofetil. Br J Dermatol 141:175–176
43. Grundmann-Kollmann M, Podda M, Ochsendorf F, Boehncke WH, Kaufmann R, Zollner TM (2001) Mycophenolate mofetil is effective in the treatment of atopic dermatitis. Arch Dermatol 137:870–873
44. Neuber K, Schwartz I, Itschert G, Dieck AT (2000) Treatment of atopic eczema with oral mycophenolate mofetil. Br J Dermatol 143:385–391
45. Benez A, Fierlbeck G (2001) Successful long-term treatment of severe atopic dermatitis with mycophenolate motefil. Br J Dermatol 144(3):638–639
46. Hansen ER, Buus S, Deleuran M, Andersen KE (2000) Treatment of atopic dermatitis with mycophenolate mofetil. Br J Dermatol 143(6):1324–1326
47. Satchell AC, Barnetson RSTC (2000) Staphylococcal septicaemia complicating treatment of atopic dermatitis with mycophenolate. Br J Dermatol 143(1):202–203
48. Jarman ER, Kuba A, Montermann E, Bartlett RR, Reske-Kunz AB (1999) Inhibition of murine IgE and immediate cutaneous hypersensitivity responses to ovalbumin by the immunomodulatory agent leflunomide. Clin Exp Immunol 115:221–228
49. Schmitt J, Wozel G, Pfeiffer C (2004) Leflunomide as a novel treatment option in severe atopic dermatitis. Br J Dermatol 150:1182–1185
50. Van Der Meer JB, Glazenburg EJ, Mulder PGH, Eggink HF, Coenraads PJ (1999) The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. Br J Dermatol 140:1114–1121
51. Hanifin J, Gupta AK, Rajagopalan R (2002) Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. Br J Dermatol 147:528–537
52. Berth-Jones J, Damstra RJ, Golsch S, Livden JK, Van Hooteghem O, Allegra F et al. (2005) Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomized, double blind, parallel group study. Br Med J 326(21):1–6
53. Kirkup ME, Birchall NM, Weinberg EG, Helm K, Kennedy CT (2003) Acute and maintenance treatment of atopic dermatitis in children—two comparative studies with fluticasone propionate (0.05%) cream. J Dermatolog Treat 14(3):141–148
54. Joly P, Roujeau J-C, Benichou J, Picard C, Dreno B, Delaporte E et al. (2002) A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. N Engl J Med 346(5): 321–327
55. O'Garra A, Vieira P (2004) Regulatory T cells and mechanisms of immune system control. Nat Med 10(8):801–805