

The Inhibitor of Costimulation of T Cells: Abatacept

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ABSTRACT. *Objective.* T cell costimulation is a key point in the regulation of immune tolerance, immune response, and autoimmunity. T cell activation does not take place upon the simple engagement of T cell receptor; a second signal is needed to fully stimulate T cells. There are a variety of molecules that can act as costimulators, and among those CD28/CD80 signaling plays a crucial role in modulating T cell response. Cytotoxic T lymphocyte antigen-4, CD152 (CTLA4) is a physiologic antagonist of CD28, and abatacept, a synthetic analog of CTLA4, has recently been approved to treat rheumatoid arthritis. An abnormal T cell activation is also believed to sustain psoriatic disease both at skin and joint sites. We aimed to evaluate the rationale of blocking CD28/CD80 signaling and the possible use of abatacept for treating psoriatic arthritis (PsA).

Methods. We reviewed the role of CD28/CD80 signaling in promoting T cell inflammation in psoriasis and the effects of CTLA4 modulation in experimental models of psoriasis and in humans.

Results. CD28/CD80 seems to be crucial in stimulating T cell activation and inflammation in psoriasis, and its inhibition by CTLA4 analogs or by anti-CD28 blocking antibodies is effective against psoriasis. Few data are available on abatacept, which seems to be valuable for the treatment of PsA but less useful in the therapy of skin psoriasis.

Conclusion. Although the CD28 molecule is crucial in activating T cells and inflammation in psoriasis, data on the efficacy of abatacept in the treatment of PsA are still not conclusive. (J Rheumatol 2012;39 Suppl 89:100–2; doi:10.3899/jrheum.120257)

Key Indexing Terms:

CD28

CTLA4

PSORIASIS

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Antigen-specific recognition by T cells through the CD3/T cell receptor complex does not activate T cells that undergo anergy. Instead a stronger stimulus by an additional signal is required to induce T cell activation¹. The human T cell antigen CD28 provides a costimulatory signal that can synergize with T cell antigen receptor stimulation in activating T cells to proliferate and secrete interleukin 2 (IL-2) and other lymphokines^{2,3}. This regulation of T cell stimulation is pivotal to prevent uncontrolled autoreactivity and to develop the immune tolerance during the maturation of the immune system. CD28 signaling is triggered by its counter receptors CD80/CD86 [expressed on antigen-presenting cells (APC)] and is regulated by a physiological antagonist (cytotoxic T lymphocyte antigen-4, CD152; CTLA4) expressed by T cells. CTLA4 binds to CD80/86 with high avidity and prevents T cell activation by blocking intracellular CD28 downstream events⁴. The inhibition of CD28-driven costimulation can be the ideal target to downregulate T cell activity in Th1-mediated diseases such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Abatacept, a CTLA4-IgG fusion protein, has been proven to be effective to treat RA⁵.

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T CELLS IN PSORIATIC DISEASE

T cells play a key role in the pathogenesis of both psoriasis and PsA. Activated T cells and APC infiltrate the dermal/epidermal junction and stimulate keratinocyte proliferation to produce IL-2 and growth factors⁶. Psoriatic T cells have enhanced expression of CD28 antigen, and its receptor, CD80, is upregulated in psoriatic lesional skin, suggesting that T cell costimulation through CD28/CD80 signaling may contribute to perpetuate T cell proliferation⁷. Besides CD28/CD80, other cell surface molecules can provide a second signal to stimulate T cells. CD2 is highly expressed on activate memory CD45RO+ T cells and binds to lymphocyte function antigen-3 (LFA-3), carried by APC to promote T cell proliferation. Activated CD45RO+ T cells have been found increased in lesional skin and synovial membrane of patients with PsA⁸ and CD2 may be a further potential target of new therapeutic strategy.

T cells also play a prominent role in the pathogenesis of PsA. T cells from the synovial fluid of patients with PsA have an activate phenotype that expresses CD69, HLA-DR, IL-2R, VLA-1 activation markers³. Immunohistochemical studies have shown T cell oligoclonal expansions in both skin and synovial membrane of patients with PsA, and therapy targeting T cells, such as cyclosporine and alefacept, have demonstrated beneficial effects in both skin and joint manifestations⁸.

INHIBITION OF T CELL COSTIMULATION

There is convincing evidence that T cells might be the ideal

target to inhibit the chronic immune response in both skin and joints of patients with psoriasis. In a short phase I/II trial, a humanized non-FcR binding derivative of the anti-human CD3 monoclonal antibody (mAb) OKT3, huOKT3 γ 1(ala-ala), was given to 7 patients with PsA, and meaningful improvement of visual analog scale pain, number of swollen and tender joints, and Psoriasis Area and Severity Index (PASI) skin score was seen at 90 days with minor adverse events⁹.

Nevertheless, it is conceivable that a prolonged and indiscriminate T cell blocking may induce a persistent immune suppression, with increase of susceptibility to infections and reduction of immune tolerance to self-antigens. Instead, a selective inhibition of T cell costimulation by targeting the second signal may prevent T cell activation and proliferation without affecting the fundamental immune functions. Alefacept, an LFA-3IgG fusion protein that inhibits T cell activation by binding to CD2 T cell surface antigen and blocking CD2/LFA-3 costimulatory signal, was given to 22 patients with psoriasis vulgaris. Clinical and histopathology outcomes were assessed up to 24 weeks. PASI score was decreased by 50% and correlated with reduction of T cells in lesional skin. Further, a significant reduction of IL-8, IL-23, interferon- γ , and inducible nitric oxide synthase messenger RNA expression was detected in lesional skin of responders¹⁰. Alefacept in combination with methotrexate (MTX) has also been proven to be effective in PsA¹¹. In our study, 185 patients were randomly assigned to receive alefacept plus MTX or placebo plus MTX. Twenty percent improvement in disease activity of the American College of Rheumatology criteria (ACR20 response) and PASI reduction were evaluated at 24 weeks. The proportion of patients achieving an ACR20 response was significantly higher in the alefacept arm (53%) than in the control one (23%, $p < 0.001$). Likewise, a decrease of PASI over 50% was more frequently observed in patients treated with alefacept (53%) than in controls (17%, $p < 0.001$)¹¹.

Several molecules have also been used to block CD28/CD80 signaling in humans and experimental models of psoriatic disease. In a first open-label phase I study, 43 patients with psoriasis vulgaris were treated with 4 intravenous injections of the chimeric fusion protein CTLA4IgG at 8 different dose levels. A 50% improvement of skin involvement was achieved in 43% of patients, and the clinical response correlated with the highest doses of CTLA4IgG, the reduction of epidermal hyperplasia¹², and the decrease of activated T cells in the skin¹³. It is likely that CTLA4IgG selectively inhibits the activation of CD4 T cell subset, as suggested by the observation that CTLA4IgG but not cyclosporine prevents the development of psoriasis and colitis in severe combined immunodeficient (SCID) mice transfected with CD45RBhi CD4 T cells¹⁴. Another approach to downmodulate the CD28/CD80 costimulatory signal is to prevent CD28 activation by blocking mAb.

Biopsies obtained from skin plaques of patients with psoriasis were grafted onto SCID mice that were then treated with FR255734 humanized anti-CD28 mAb. Histology of the plaques showed a striking reduction of the number of infiltrating T cells and of activated HLA-DR⁺ T cells. Further, FR255734 was capable of blocking T cell proliferation and proinflammatory cytokine production *in vitro*¹⁵.

Abatacept is a fully human fusion protein made by the extracellular domain of CTLA4 linked to the Fc portion of human IgG1 and has been approved for the treatment of RA⁵. Recently, a randomized double-blind clinical trial assessed the efficacy of abatacept in PsA¹⁶. PsA patients with active joint disease and active plaque psoriasis despite treatment with disease-modifying antirheumatic drugs (DMARD) or anti-tumor necrosis factor (TNF) drugs were randomized to receive abatacept at different dose regimens or placebo. After 6 months, the percentage of patients achieving an ACR20 response was significantly higher in the abatacept (10 mg/kg) group than in controls. The structural joint damage evaluated by magnetic resonance imaging developed further in the placebo group but was reduced in patients treated with abatacept. With regard to psoriasis, a reduction of skin involvement was obtained regardless of the abatacept dose, but a meaningful investigator's global assessment response was seen only with 3 mg/kg of abatacept. Different causes may account for this unexpected result. The small size of the population, the short duration of the observation, and the inclusion of patients previously treated with TNF inhibitors may have influenced the skin response. However, the paradoxical better skin response to low-dose abatacept may be explained by an immunological rationale. In a mouse model of psoriasis, it has been shown that increasing doses of psoralen ultraviolet A (PUVA) improve psoriasis through induction of foxp3⁺ regulatory T cells that suppress skin inflammation. The activation of foxp3⁺ regulatory T cells is mediated by CTLA4 signaling, and treatment with anti-CTLA4 mAb stops the activation of these cells and the beneficial effect of PUVA¹⁷. The previous findings of a negative correlation between skin response and abatacept doses may be due to the suppression of regulatory T cells at higher doses.

CONCLUSIONS

Costimulatory signals play a major role in activating T cells in both skin and synovial membrane in psoriasis. CD28/CD80/CTLA4 modulation may downregulate immune response and inflammation. Abatacept seems to be promising for the treatment of PsA, but further studies on larger cohorts of patients are needed to better assess the skin response.

REFERENCES

1. Harding FA, McArthur JG, Gross JA, Raulet DH, Allison JP. CD28-mediated signalling co-stimulates murine T cells and prevents induction of anergy in T-cell clones. *Nature* 1992;356:607-9.

2. Nunes J, Klasen S, Franco MD, Lipcey C, Mawas C, Bagnasco M, et al. Signalling through CD28 T-cell activation pathway involves an inositol phospholipid-specific phospholipase C activity. *Biochem J* 1993;293 Part 3:835-42.
3. Iannone F, Corrigan VM, Kingsley GH, Panayi GS. Evidence for the continuous recruitment and activation of T cells into the joints of patients with rheumatoid arthritis. *Eur J Immunol* 1994;24: 2706-13.
4. Ellis JH, Burden MN, Vinogradov DV, Linge C, Crowe JS. Interactions of CD80 and CD86 with CD28 and CTLA4. *J Immunol* 1996;156:2700-9.
5. Korhonen R, Moilanen E. Abatacept, a novel CD80/86-CD28 T cell co-stimulation modulator, in the treatment of rheumatoid arthritis. *Basic Clin Pharmacol Toxicol* 2009;104:276-84.
6. Demidem A, Taylor JR, Grammer SF, Streilein JW. T-lymphocyte-activating properties of epidermal antigen-presenting cells from normal and psoriatic skin: evidence that psoriatic epidermal antigen-presenting cells resemble cultured normal Langerhans cells. *J Invest Dermatol* 1991;97:454-60.
7. Nickoloff BJ, Nestle FO, Zheng XG, Turka LA. T lymphocytes in skin lesions of psoriasis and mycosis fungoides express B7-1: a ligand for CD28. *Blood* 1994;83:2580-6.
8. Choy E. T cells in psoriatic arthritis. *Curr Rheumatol Rep* 2007;9:437-41.
9. Utset TO, Auger JA, Peace D, Zivin RA, Xu D, Jolliffe L, et al. Modified anti-CD3 therapy in psoriatic arthritis: a phase I/II clinical trial. *J Rheumatol* 2002;29:1907-13.
10. Chamian F, Lowes MA, Lin SL, Lee E, Kikuchi T, Gilleaudeau P, et al. Alefacept reduces infiltrating T cells, activated dendritic cells, and inflammatory genes in psoriasis vulgaris. *Proc Natl Acad Sci U S A* 2005;102:2075-80.
11. Mease PJ, Gladman DD, Keystone EC; Alefacept in Psoriatic Arthritis Study Group. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2006;54:1638-45.
12. Abrams JR, Lebwohl MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS, et al. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. *J Clin Invest* 1999;103:1243-52.
13. Abrams JR, Kelley SL, Hayes E, Kikuchi T, Brown MJ, Kang S, et al. Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. *J Exp Med* 2000;192:681-94.
14. Davenport CM, McAdams HA, Kou J, Mascioli K, Eichman C, Healy L, et al. Inhibition of pro-inflammatory cytokine generation by CTLA4-Ig in the skin and colon of mice adoptively transplanted with CD45RBhi CD4+ T cells correlates with suppression of psoriasis and colitis. *Int Immunopharmacol* 2002;2:653-72.
15. Raychaudhuri SP, Kundu-Raychaudhuri S, Tamura K, Masunaga T, Kubo K, Hanaoka K, et al. FR255734, a humanized, Fc-Silent, anti-CD28 antibody, improves psoriasis in the SCID mouse-psoriasis xenograft model. *J Invest Dermatol* 2008;128:1969-76.
16. Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis Rheum* 2011;63:939-48.
17. Singh TP, Schön MP, Wallbrecht K, Michaelis K, Rinner B, Mayer G, et al. 8-methoxypsoralen plus ultraviolet A therapy acts via inhibition of the IL-23/Th17 axis and induction of Foxp3+ regulatory T cells involving CTLA4 signaling in a psoriasis-like skin disorder. *J Immunol* 2010;184:7257-67.