CHAPTER 2

ABATACEPT

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Abatacept (Orencia™) is a novel biologic agent that is a fully human fusion protein made by the extracellular domain of cytotoxic T-lymphocyte antigen (CTLA)4 linked to the Fc portion of human IgG1 and has been approved for the treatment of rheumatoid arthritis (RA) and juvenile idiopatic arthritis.[1-3] It blocks activation of T cells by blocking the CD80/CD86:CD28 co-stimulatory signal from antigen-presenting cells by blocking binding of B7 protein on antigen-presenting cells.(3) As an indirect effect within the inflammatory cascade, the production of cytokines and autoantibodies is inhibited.[4,5] In clinical trials with abatacept at doses approximating 10mg/kg, decreases were observed in serum levels of soluble interleukin-2 receptor, interleukin-6, rheumatoid factor, C-reactive protein, matrix metalloproteinase-3 and TNFα.[6]

Abatacept for psoriasis and psoriatic arthritis: Psoriasis vulgaris is an inflammatory skin disease. Cytokines released from the activated T cells are believed to contribute to the pathologic changes induced in lesional keratinocytes and vascular endothelium in psoriasis.[7] Firstly Abrams et al investigated the role of the CD28/CTLA-4 pathway in psoriasis vulgaris in a 26-week, phase I study. Forty-three psoriatic patients received four infusions of the soluble chimeric protein CTLA4-Ig, 46% of these patients achieved a 50% or greater improvement correlated with the reduction in epidermal hyperplasia and skin-infiltrating T cells.[8]

Mease P. et al[9] performed a phase II study in 170 psoriatic arthritis patients with psoriatic skin lesions. The patients received placebo or three different dosage regimens of abatacept. Abatacept-treated patients received 3mg/kg, 10mg/kg or 30/10mg/kg (two initial doses of 30mg/kg, followed by 10mg/kg) on days 1, 15 and 29 and then once every 28 days thereafter until 169th day. By means of improvement in psoriatic arthritis American College of Rheumatology 20% response was significant compared with placebo in the groups receiving abatacept 10mg/kg and 30/10mg/kg but not 3mg/kg. Improvements in the psoriasis area and severity index (PASI) 50 response were observed in all abatacept regimens. On day 169, the proportions of patients achieving a PASI50 response were 43% at 3mg/kg, 29% at 10mg/kg, 35% at 30/10mg/kg and 14% for placebo. On day 169, PASI75 response were 38% at 3mg/kg, 14% at 10mg/kg, 10% at 30/10mg/kg and 5% for placebo; with only those taking the 3mg/kg dose of abatacept showed improvement compared to placebo. On day 169, investigator's global assessment response (lesions judged to be "clear or almost clear") were 38% of those taking 3mg/kg of abatacept, 25% taking 10mg/kg, 21% taking 30/10mg/kg and %26 taking placebo, with only the 3mg/kg group showing a modest improvement compared to placebo. Interestingly psoriatic skin response was seen optimum in 3mg/kg dose conversely to recommended dose for psoriatic arthritis and romatoid arthritis. Authors commented that the different effects of abatacept on the joints and the skin may indicate the inflammation in the skin differs from that in the joints. Additionally authors also pointed that the highest PASI75 response was 38% while other studies with anti-TNF agents PASI75 response was up to 68%.[10,11,12] On the other hand the subjects included in this study were inadequate responsed patients to anti-TNF therapy may have resulted in a more treatment-resistant population and may thus have lessened the abatacept response.

In an other study Varada et al[13] retrospectively evaluated 96 patients given the diagnoses of psoriasis and lupus erythematosus. In this study there were three patients receiving abatacept. All three patients had SLE, chronic plaque psoriasis and psoriatic arthritis. Improvements in SLE symptoms and cutaneous psoriasis were noticed while cutaneous photosensitivity was reported in two of three patients.

Ursini et al[4] report a psoriatic arthritis patient with vulvar psoriatic lesions. Though they report that patient disease activity score was significantly reduced three months after the initiation of abatacept treatment, they did not point psoriatic skin lesions enough if the lesions cleared or not.

Rodriges et al[14] used abatacept (two infusions, with a 20-day interval) for DMARDS and anti-TNF resistant psoriatic arthritis; beside joint symptoms they also report the improvement of psoriatic skin lesions, anemia and inflammatory markers.

Also there are uncompleted studies investigating the combination of abatacept with other biologicals for psoriasis. A phase II study was started at February 2014,

estimated completion date February 2016, officially titled as "a pilot study of the safety and efficacy of abatacept injections in the treatment of mucocutaneous manifestations of Behcet's syndrome" investigating the efficacy of abatacept treatment in Behçet's disease.[39]

There is a newly started phase I study, officially titled as "open-label pilot study of abatacept for the treatment of vitiligo" estimated completion date January 2017 investigating vitiligo lesions improvement by weekly injections of abatacept.[40]

DOSAGE

For RA treatment, an initial dose of approximately 10 mg/kg iv, repeated by additional doses after 2 and 4 weeks, with further doses every 4 weeks. After the initial intravenous dose, 125 mg subcutaneous injection 24 hours later, repeated by weekly subcutaneous injections of 125mg is an other choice of the abatacept treatment.[41,42] Merrill used the same protocol as desribed above for patients with RA in a phase II study for SLE patients, and reported efficacy of abatacept in SLE.[25]

Adverse events and safety: Adverse effects of abatacept include increased risk of infections and malignancies. All patients should be screened for tuberculosis and hepatitis B and C before treatment, live attenuated vaccines should be avoided during therapy. Infusion reactions include dizziness, headache, nausea, fever and hypertension. In a study of long-term safety, 96% of patients experienced adverse events; however, most of them were mild to moderate. No significant differences in adverse events were noted when the abatacept group and placebo group (receiving DMARDs only) were compared.[43] The other studies showed that; the risk of apperance of tumors in patients treated with abatacept is not higher to what is expected in RA patients; the use of abatacept in patients with stage IV heart failure must be approached with caution; in patients with demyelinating disease, the use of abatacept is not contraindicated; in case of use, close neurological follow up is needed.[44-47] Pregnancy category of abatacept is C.[(6)] Abatacept should be avoided in patients receiving TNF antagonist, such as adalimumab, etanercept and infliximab because such combination therapy may increase the risk for severe infections.[6]

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