CHAPTER 3

ADALIMUMAB IN DERMATOLOGY

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Adalimumab (ADA) is a recombinant, fully humanized IgG1 monoclonal antibody targeted against TNF-α. and. It has been in use since 2003 and is an increasingly important drug in dermatology. Treatment with ADA proved to be effective for the management of chronic moderate to severe plaque-type psoriasis in patients whose disease had been refractory to systemic conventional therapies. Pivotal trials such as CHAMPION, REVEAL have proved this biological agent to be generally safe and well tolerated by patients.[1,2] Besides psoriasis, ADA was approved by FDA for use in psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis[3].

After subcutaneous administration of a single 40-mg dose, ADA's absorption and distribution is slow, with peak concentrations reached 5 days after administration. The terminal half-life of ADA is between 10 and 20 days.[4]

In the management of chronic moderate to severe plaque-type psoriasis, the FDA-approved standard dosing regimen for ADA is an initial dose of 80 mg at week 0 that is followed by 40 mg every other week starting at week 1. According to a study, the therapy should be reconsidered in a patient not responding within 12 weeks regarding dose escalation. It was reported that, dose escalation to 40 mg once a week improves clinical response in non-responders to standard therapy.[5] When the relapse occured after withdrawal of the drug, it was reported that there was a good likelihood of regaining clinical efficacy following ADA reinitiation.[6]

The production of antibodies to ADA in autoimmune patients treated with ADA has been shown to diminish treatment efficacy.[1]

Adalimumab (ADA) is generally considered safe and well tolerated. The most common side effects of ADA are injection site reactions.[7-9] Rare but serious adverse effects such as demyelination, infection, lymphoma, non-melanoma skin cancer, cardiovascular complications, hepatitis have been observed.[8-14]

A report of results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) which comparing the infection risk of the most used psoriatic biologic agents across patients, suggests that treatment with ADA and infliximab are associated with a higher risk for serious infections than nonmethotrexate and non-biologic therapies.[16] Therefore, attention to specific aspects of patient management such as prescreening requirements and symptoms to watch for is required to reduce risk.

In psoriais treatment, combination therapy of ADA, like the other biologics, with topicals, traditional systemics, phototherapy, may enhance efficacy and can permit discontinuation or dose reduction of traditional systemic agents. Combination therapy seems better rather than changing biologic agents, in circumstances of inadequate efficacy or relapses with monotherapy.

Numerous case reports suggest ADA could be helpful in treating some skin disorders other than psoriasis, such as Behçet's Disease (BD), hidradenitis suppurativa, pyoderma gangrenosum, pemphigus, cutaneous sarcoidosis and aphthous stomatitis.

TNF-α is believed to be a central inflammatory mediator in Behçet's Disease (BD). ADA therapy is reported to be successful in treating BD with different manifestations.[15-24]

Arida et al. analyzed published data on anti-tumor necrosis factor TNF agents' efficacy on 369 Behcet's disease patients from 20 different countries who were refractory to conventional therapies They found 13 articles on ADA reporting on 28 patients.[25] In these patients, prompt remission of oral ulcers, genital ulcers, erythema nodosum, and other skin lesions was noted to be induced in 73%, 86%, 100%, and 80%, respectively. Regarding the therapeutic efficacy of ADA on ocular involvement, switching from infliximab to ADA in 2 patients due to advers reactions, was noted to be successful with complete remission. They noted that 3 patients with gastrointestinal involvement were treated succesfully with ADA.[21,26]

Perra D et al. evaluated 19 patients with severe clinical manifestations of BD who unresponsive to immunosupressive therapy including TNF-alpha inhibitors (five had received infliximab and two had Etanercept) or suffered from adverse effect of previous drugs.[27]

progress to fibrosis. It appears that TNF α serves as a mediator of cell signaling in various immune responses, rather than for a specific immune response. Thus, the actions of TNF α likely depend upon its interaction with surrounding cells and cytokines.[70,71]

ADA seems to be more effective than Etanercept in the treatment of cutaneous sarcoidosis.[64,72,73] In the case of Field et al. which was a recalcitrant cutaneous sarcoidosis and didn't respond to Etanercept; the combination of ADA, methotrexate and prednisolone resulted in clearing of cutaneous sarcoidosis at all sites[73]. Burns AM et al. presented a patient, who had resolution of Etanercept-induced cutaneous and pulmonary sarcoid-like granulomas, following replacement with ADA.[74]

When it comes to Infliximab, regarding that it is delivered intravenously in the physician's office, treatment with ADA has advantages over infliximab: ADA can be administered by the patient at home, which most patients find it to be convenient.

In regard to side effects, TNF-blocking agents seems to be superior to other immunsupressive treatments described for sarcoidosis such as steroids, methotrexate, azathioprine, cyclosporin, cyclophosphamide and leflunomide.[61]

In selected cases ADA may be beneficial for the treatment of cutaneous and/or systemic sarcoidosis but prospective randomized controlled trials on larger series will be necessery to asses objectively the efficacy of ADA **in** sarcoidosis skin lesions,.

Pemphigus

Because Tumor necrosis factor- α causes aggregation and augmented responses of neutrophils which are responsible for the acantholysis of the epidermis, it is logical to expect TNF-α blokers may improve pemphigus. Howell SM et al reported a patient with IgA pemphigus who failed multiple treatments, completely cleared after the third dose of ADA. It was applied at a dose of 40 mg biweekly together with Mycophenolate mofetil (1 gm daily), which had been started 2 weeks prior with no significant improvement as monotherapy.[75] Vojáčková et al. reported a patient with pemphigus, to whom ADA was administered because of the inadequate effect of combined immunosuppressive therapy (steroids+azathioprine+ cyclophosphamide) and noted to achieve a very good clinical response.[76] In the literature, a case with IgA Pemphigus unresponsive to multipl drug therapies, has been noted to show partial remission with ADA 40 mg biweekly.[77] In addition to these diseases mentioned above, there have been some case reports describing off-label use of ADA that show possible indications such as Sweet's Syndrome, Wegener Granulomatosis, connective tissue diseases, multicentric reticulohistiocytosis, GVHD, subcorneal pustular dermatosis and lichen planus.[78-80]

Conclusion:

ADA is an increasingly important drug in dermatology. Combination therapy of biologics with topicals, phototherapy, and/or conventional systemics may enhance efficacy including speed of onset and maintenance of response. ADA has also been shown to improve patients' life quality significantly. Although available data indicate that ADA is safe and well tolerated because of its rare but severe side effects and expensivity, attention to specific aspects of patient management (ie, prescreening requirements, symptoms to watch for) is required to reduce risk

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