The Journal of Medical Research

Review Article

JMR 2017; 3(2): 82-85
March- April
ISSN: 2395-7565

www.medicinearticle.com
Received: 09-01-2017
Accepted: 22-04-2017

Benefits vs. side effects of Adalimumab treatment in Psoriasis/Psoriatic Arthritis

Suad Hannawi[1], *Issa Al Salmi*[2]

1 *Associate Professor, Ministry of Health and Prevnetion, United Arab Emirates*
2 *Royal Hospital, Muscat, Oman*

Abstract

Psoriatic Arthritis (PsA) is a seronegative, inflammatory joint disease. In most patients with PSA, skin psoriasis precedes arthritis; however, the causality is multi-factorial and many aspects related to it remain unclear. Tumor necrosis factor (TNF) plays essential role in the pathogenesis of PsA and psoriasis. Hence, the selective inhibition of TNF-α leads to significant improvement of disease activity in patients with immunologically mediated inflammation such as psoriasis and PsA. Adalimumab has been demonstrated to improve functional and dermatological-related limitations. However, not all patients have a good response to Adalimumab, and the long-term safety remains unknown. In this literature review we are highlighting the benefits versus possible side effect of adalimumab in treating psoriatic arthritis and psoriasis.

Keywords: Psoriatic arthritis, Psoriasis, Tumor necrosis factor, Tumor necrosis factor blockers, Aadalimumab.

INTRODUCTION

Psoriasis is an emotionally and physically debilitating disease that has a significantly negative impact on an affected person's quality of life. In addition, among those who have psoriatic arthritis (PsA), more than 50% experience progressive, erosive arthritis that is often accompanied by functional impairment. The functional impairments that associated with psoriasis and PsA are associated with increase healthcare costs, impaired health-related quality of life and substantial work-related disability, including a lower rate of employment**.**

In an effort to improve treatment for patients who suffer from these diseases, researches had led to the discovery of several new therapies that directly target the immune response that drives psoriasis/PsA. One specific protein that has proven as an effective target for therapy is tumor necrosis factor-alpha (TNF-α).

Adalimumab is the first fully humanized monoclonal antibody targeted against TNF. The Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) demonstrated that Adalimumab significantly improve cutaneous and joint manifestations, lessen disability caused by joint damage, inhibit structural changes on radiographs and improve health-related quality of life (HRQOL) among PsA patients. However, not all patients have a good response to Adalimumab, and the long-term safety remains unknown. Further, there are minimal data published regarding factors that can identify patients most likely to respond to Adalimumab or to show disease remission.

Literature review

Psoriasis is a chronic inflammatory disease that affects approximately 2–3% of the world's population. It has a complex pathophysiology and a multigenic background. Autoimmunity and genetic hallmarks combine to confer the disease, which is characterized by chronic plaques (85-90% of all cases) and/or PsA (from 5 to >30% of patients with psoriasis [1], that involve the peripheral and sacro-iliac joints, nails, and skeleton) [2].

Despite the encouraging results of studies looked at Adalimumab treatment in psoriasis and PsA, others reported a new onset or aggravation of psoriatic skin lesions after Adalimumab treatment onset [3].

***Corresponding author:**
Dr. Suad Hannawi
Associate Professor, Ministry of Health and Prevnetion, United Arab Emirates
Tel: + 971505516624
Email: suad1[at]ausdoctors.net

TNF-α has a key element (with T cells) role in the pathogenesis of psoriasis and PsA [4]. It's a naturally occurring cytokines in the skin, and is involved in numerous normal and abnormal inflammatory immune. TNF-α induce the synthesis of adhesion molecules on endothelial cells and keratinocytes, thereby influences cellular infiltration in the skin. It also has a direct effect on the abnormal keratinoctye proliferation and maturation seen in psoriatic lesions [5]. TNF-α production and activity are elevated in the 1-lesional psoriatic skin compared with non-lesional psoriatic skin and non-psoriatic skin [6-9], 2-serum of individuals with psoriasis than those without it, and in the 3-synovial fluid of individuals with PsA [10-12]. Those lesional and serum TNF-α levels correlate positively with psoriasis area and PsA severity index (PASI) [8].

Adalimumab is a recombinant, fully human and highly specific IgG1 monoclonal antibody targeted against TNF. It produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps.

Adalimumab was first administered to a study patient in 1997. The recommended dosage of Adalimumab is 40 mg administered every other week as a subcutaneous (s.c) injection for PsA. In psoriasis, Adalimumab is administered SC at a dose of 80 mg the first week, followed by 40 mg the next week and every other week thereafter.

The average absolute bioavailability estimated from three studies following a single 40-mg dose was 64%. After doses of 0.5 kg−1 (~40 mg), clearances ranged from 11 to 15 ml h−1, and the distribution volume ranged from 5 to 6 l [13]. Once it is given, the drug reaches its peak level at 5½ days, with a half-life of approximately 14 days [14].

The slow absorption rate following SC administration, slow elimination rate, and appropriate dosing frequency give Adalimumab a smooth and uniform concentration-time profile, minimizing the occurrences of overexposure and resultant adverse events, as well as underexposure and consequent symptom recurrence [15,16]. Clinical response to Adalimumab is substantial and rapid, with statistically significant improvement in Psoriasis Area Severity Index (PASI) occurring as early as 1 week after initiation of treatment [17,18].

The majority of responses attributed to TNF are regulated by the p55 cell surface TNF receptors. Upon binding to TNF-α, Adalimumab blocks its interaction with the p55 and p75 cell surface TNF receptors, this lead to inhibition of several TNF-alpha-induced events. Hence, it rapidly reduces serum concentrations of acute-phase reactants (such as C-reactive protein and erythrocyte sedimentation rate), interleukin-6, and serum levels of metalloproteinases (MMP-1 and MMP-3) which is involved in joint destruction by 50% [19], More, it reduce expression of adhesion molecules responsible for leukocyte migration and restore the density of epidermal Langerhans cells in psoriatic skin lesions [20]. Interestingly, the reduction of the absolute number and density of epidermal Langerhans cells had been found in untreated psoriatic skin as compared to uninvolved skin from psoriatic patients [21].

As a result the process of neutralization of TNF-α by a specific monoclonal antibody both skin and joint manifestations of psoriasis/psoriatic arthritis improve. CHAMPION study showed that using adalimumab compared to Methotrexate (MTX) or placebo in a comparative analysis resulted in greater improvement in quality of life among Adalimumab group. It was reflected in all Dermatology Life Quality Index (DLQI) components; symptoms and feelings, daily activities, leisure, work/school, personal relationships and treatment [22]. More, Adalimumab lowered pain and itching and gave better disease control compared to Methotrexate. Another study included patients with moderate to severe psoriasis showed that a 12 weeks treatment with Adalimumab (40 mg weekly or every other week) versus placebo resulted in significant improvement in DLQI, European Quality of Life-5 Dimensions (EQ-5D), Sort Form-36 (SF-36), Mental Component Summary scores, Bodily Pain, Vitality, Social Functioning, Role-Emotional, and Mental Health domains [23]. Furthermore, a study looked at the predictors of treatment response and to achieve remission in PsA patients receiving anti-TNF blocker showed that being female resulted in lower response rates to treatment and to achieving remission [24]. No reason has been given to why the female patients have a lower response to treatment.

Adalimumab, is usually well tolerated. In studies of Rheumatoid arthritis (RA) patients that included >10,050 cases of RA, representing 12 506 patient-years, in <10% of cases therapy was discontinued because of the adverse events [25]. The most frequent side effect observed with Adalimumab treatment was injection site reaction, which is generally mild to moderate and transient, and do not require drug discontinuation. In placebo-controlled trials, injection site reactions were reported in 17%–20% of patients treated with Adalimumab (versus 11%–14% of patients receiving placebo) [26]. Other dermatological side effects reported with Adalimumab treatment include skin infections (the most common among dermatological manifestations), eczema, drug-related eruptions, tumors, actinic keratosis, vasculitis, ulcers and psoriasis (or psoriasiform eruptions). The latter been described in a case series of 12 RA patients [27], where two cases developed Adalimumab treatment-related plaque psoriasis and plantar pustulosis.

In the CHAMPION study, adverse events were of similar frequency in Adalimumab, MTX and placebo groups (73.8, 80.9 and 79.2%, respectively) and were mainly mild to moderate. Percentages of serious adverse events were 1.9, 0.9 and 1.9%, respectively [19]. And, in the REVEAL study; 0.6% of patients treated with Adalimumab experienced serious adverse events vs. 1.0% in the placebo group 26.

Due to the central role of TNF in the host defense mechanism, a major concern with TNF-blockers is the increase risk of infections and malignancies [28,29]. The most important infectious complication is the reactivation of tuberculosis (TB), whose incidence has decreased following implementation of TB screening [25]. Generally, TB reactivation of a latent form occurs within the first 8 months of treatment. In post-marketing experience other opportunistic infections have been reported as well. The most common infections were bronchitis, upper respiratory tract and urinary tract infections. More, Adalimumab cause a twofold increased incidence of rare infections such as fungal pneumonia, septic arthritis or pyelonephritis [28]. On the other hand, the rate of serious infections in Adalimumab RA trials was within the range reported in RA populations (3.1–9.6/100 patient-years) [30]. Dixon et al did not find increased rates of serious infections in patients with RA in the anti-TNF cohort of the British Society for Rheumatology Biologics Registry when considering the entire duration of therapy, but noted an increased early risk (within the first 90 days of therapy commencement) compared with the disease modifying anti-rheumatic drug cohort [31]. There are data suggesting risk of hepatitis-B reactivation in Adalimumab patients. On the other hand, many reports have stated that anti-TNF-α treatment in hepatitis-C is safe and well tolerated by patients [32].

The potential role of TNF inhibitors in the development of malignancies is not known. The risk of malignancies with Adalimumab in global clinical trials was not increased when compared with the general population. More, adverse event reporting and cohort studies have failed to demonstrate any linkage between the development of solid tumors and anti-TNF therapy RA [25,29].

Patients with chronic inflammatory diseases, such as RA, are known to be at higher risk for the development of lymphoma, with twofold increase the risk of occurrence of lymphomas over that in the general population, that is correlated with longstanding high disease activity [33]. In trials of patients with RA treated with Adalimumab [25], the standardized incidence rate of lymphomas was 3.19. So the precise

answer to the question of the role of Adalimumab in lymphomas will have to await future analyses.

Approximately 3–12% of patients treated with Adalimumab develop autoantibodies to antinuclear and double-stranded (ds) DNA, however, development of a lupus-like syndrome appears to be uncommon. Due to the frequent occurrence of autoantibodies during anti-TNF therapy (only 13 cases of systemic lupus erythematosus and lupus-like syndromes in 12 506 patient-years of Adalimumab exposure have been reported) [33]. They are considered without clinical relevance, unless symptoms suggestive of lupus-like syndrome develop. Therefore, measurement of anti-nuclear antibodies and anti-dsDNA is not required during treatment with TNF-alpha antagonists [34].

Further reported side effects of Adalimumab are fever, flushing, interstitial pneumonitis or fibrosis, leukocytoclastic vasculitis, menorrhagia, and blood dyscrasias, including thrombocytopenia, leukopenia and pancytopenia [17,26,29,35].

Other safety problems rarely associated with TNF-blockers, including Adalimumab, are represented by new onset or exacerbation of congestive heart failure (CHF). About 44 out of 10,006 patients in RA trial reported a medical history of CHF, 7% of whom reported CHF events in a period of trials. Also, worsening or initiation of demyelinating conditions, especially multiple sclerosis (MS) had been reported as a safety concern related to Adalimumab [28,29]. Both RA and psoriasis are thought to increase the risk of multiple sclerosis [33].

Contraindications for Adalimumab use include chronic, active, serious, and recurrent infection, active TB (appropriate screening tests should be performed in all patients), latent TB in the absence of chemoprophylaxis, reactivation of hepatitis B, multiple sclerosis and other demyelinating disease, first-degree relative with MS, moderate to severe heart insufficiency (New York Heart Association; NYHA class III and IV CHF), pregnancy or lactation, and hypersensitivity to Adalimumab or its ingredients. During treatment with Adalimumab, patients should avoid live and live-attenuated vaccines [36].

Although the available evidences support the favorable safety profile of biologic agents for psoriasis, long-term follow-up in large sample populations is required to obtain more defined data, particularly about uncommon adverse events and exacerbation of current disease. More, Burmester et al evaluated safety data from approximately 10 years of clinical trial experience with Adalimumab in six diseases including PsA, they reported that it is safe for long-term use. Given the confirmed efficacy and substantial benefits of Adalimumab in these conditions, the risk of therapy should be weighed against the risk of uncontrolled inflammatory disease and its long-term sequel [37].

In the meantime, a positive risk/benefit ratio may be preserved through careful selection of patients and monitoring, based on the recommendations of the concerned authority and consensus guidelines.

CONCLUSİON

The available large analyses of Adalimumab safety are mainly based on trials of patients with RA. Less Data provided with observations made during studies on treating psoriasis or PsA. Thereafter, a careful approach is needed in psoriasis/PSA therapy, which is obviously differs than RA.

Competing interests

The authors declare that they have no competing interests.

REFERENCES

1. Mease PJ. Tumour necrosis factor (TNF) in psoriatic arthritis: pathophysiology and treatment with TNF inhibitors. Annals of the rheumatic diseases. 2002;61:298-304.
2. Ayroldi E, Bastianelli A, Cannarile L, Petrillo MG, Delfino DV and Fierabracci A. A pathogenetic approach to autoimmune skin disease therapy: psoriasis and biological drugs, unresolved issues, and future directions. Current pharmaceutical design. 2011;17:3176-90.
3. Kary S, Worm M, Audring H, Huscher D, Renelt M, Sorensen H, Stander E, Maass U, Lee H, Sterry W and Burmester GR. New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving tumour necrosis factor alpha antagonists. Annals of the rheumatic diseases. 2006;65:405-7.
4. Griffiths CE and Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370:263-71.
5. Gottlieb AB. Infliximab for psoriasis. Journal of the American Academy of Dermatology. 2003;49:S112-7.
6. Nickoloff BJ, Karabin GD, Barker JN, Griffiths CE, Sarma V, Mitra RS, Elder JT, Kunkel SL and Dixit VM. Cellular localization of interleukin-8 and its inducer, tumor necrosis factor-alpha in psoriasis. The American journal of pathology. 1991;138:129-40.
7. Uyemura K, Yamamura M, Fivenson DF, Modlin RL and Nickoloff BJ. The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response. The Journal of investigative dermatology. 1993;101:701-5.
8. Bonifati C, Carducci M, Cordiali Fei P, Trento E, Sacerdoti G, Fazio M and Ameglio F. Correlated increases of tumour necrosis factor-alpha, interleukin-6 and granulocyte monocyte-colony stimulating factor levels in suction blister fluids and sera of psoriatic patients--relationships with disease severity. Clinical and experimental dermatology. 1994;19:383-7.
9. Ettehadi P, Greaves MW, Wallach D, Aderka D and Camp RD. Elevated tumour necrosis factor-alpha (TNF-alpha) biological activity in psoriatic skin lesions. Clinical and experimental immunology. 1994;96:146-51.
10. Partsch G, Steiner G, Leeb BF, Dunky A, Broll H and Smolen JS. Highly increased levels of tumor necrosis factor-alpha and other proinflammatory cytokines in psoriatic arthritis synovial fluid. The Journal of rheumatology. 1997;24:518-23.
11. Ritchlin C, Haas-Smith SA, Hicks D, Cappuccio J, Osterland CK and Looney RJ. Patterns of cytokine production in psoriatic synovium. The Journal of rheumatology. 1998;25:1544-52.
12. Danning CL, Illei GG, Hitchon C, Greer MR, Boumpas DT and McInnes IB. Macrophage-derived cytokine and nuclear factor kappaB p65 expression in synovial membrane and skin of patients with psoriatic arthritis. Arthritis and rheumatism. 2000;43:1244-56.
13. Traczewski P and Rudnicka L. Adalimumab in dermatology. British journal of clinical pharmacology. 2008;66:618-25.
14. den Broeder A, van de Putte L, Rau R, Schattenkirchner M, Van Riel P, Sander O, Binder C, Fenner H, Bankmann Y, Velagapudi R, Kempeni J and Kupper H. A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. The Journal of rheumatology. 2002;29:2288-98.
15. Nestorov I. Clinical pharmacokinetics of TNF antagonists: how do they differ? Seminars in arthritis and rheumatism. 2005;34:12-8.
16. Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. The Journal of rheumatology Supplement. 2005;74:13-8.
17. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, Heffernan M, Miller B, Hamlin R, Lim L, Zhong J, Hoffman R and Okun MM. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. Journal of the American Academy of Dermatology. 2006;55:598-606.
18. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, Unnebrink K, Kaul M, Camez A and Investigators CS. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). The British journal of dermatology. 2008;158:558-66.
19. Shukla R and Vender RB. Pharmacology of TNF inhibitors. Basel: Birkhäuser Verlag, Swizerland: B.R. Weinberg JM, editors; 2006.
20. Mease PJ. Adalimumab: an anti-TNF agent for the treatment of psoriatic arthritis. Expert opinion on biological therapy. 2005;5:1491-504.
21. Gordon KB, Bonish BK, Patel T, Leonardi CL and Nickoloff BJ. The tumour necrosis factor-alpha inhibitor adalimumab rapidly reverses the decrease in epidermal Langerhans cell density in psoriatic plaques. The British journal of dermatology. 2005;153:945-53.
22. Katugampola RP, Lewis VJ and Finlay AY. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. The British journal of dermatology. 2007;156:945-50.
23. Shikiar R, Heffernan M, Langley RG, Willian MK, Okun MM and Revicki DA.

Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial. The Journal of dermatological treatment. 2007;18:25-31.
24. Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL and Bsrbr. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. Rheumatology. 2010;49:697-705.
25. Schiff MH, Burmester GR, Kent JD, Pangan AL, Kupper H, Fitzpatrick SB and Donovan C. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Annals of the rheumatic diseases. 2006;65:889-94.
26. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, Strober BE, Kaul M, Gu Y, Okun M and Papp K. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. Journal of the American Academy of Dermatology. 2008;58:106-15.
27. Aslanidis S, Pyrpasopoulou A, Douma S and Triantafyllou A. Tumor necrosis factor-a antagonist-induced psoriasis: yet another paradox in medicine. Clinical rheumatology. 2008;27:377-80.
28. Scheinfeld N. Adalimumab: a review of side effects. Expert opinion on drug safety. 2005;4:637-41.
29. Desai SB and Furst DE. Problems encountered during anti-tumour necrosis factor therapy. Best practice & research Clinical rheumatology. 2006;20:757-90.
30. Doran MF, Crowson CS, Pond GR, O'Fallon WM and Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis and rheumatism. 2002;46:2287-93.
31. Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, British Society for Rheumatology Biologics Register Control Centre C, Silman AJ and British Society for Rheumatology Biologics R. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis and rheumatism. 2007;56:2896-904.
32. Jackson JM. TNF- alpha inhibitors. Dermatologic therapy. 2007;20:251-64.
33. Salfeld J and Kupper H. Adalimumab. Biologics in General Medicine. 2007:14-31.
34. Vena GA and Cassano N. Drug focus: adalimumab in the treatment of moderate to severe psoriasis. Biologics : targets & therapy. 2007;1:93-103.
35. Mossner R, Schon MP and Reich K. Tumor necrosis factor antagonists in the therapy of psoriasis. Clinics in dermatology. 2008;26:486-502.
36. Bahner JD, Cao LY and Korman NJ. Biologics in the management of psoriasis. Clinical, cosmetic and investigational dermatology. 2009;2:111-28.
37. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M and Lipsky P. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354:1932-9.