



Case Report

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Successful Usage of Combination Biologic Therapy with Etanercept and Actemra for the Treatment of TNF Inhibitor Failure Patients with Rheumatoid Arthritis: A Report of 2 Cases



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Abstract

In the treatment of patients with rheumatoid arthritis with anti-tumour necrosis factor therapy, it is not uncommon for some patients to be unresponsive or relapse with treatment. We report the successful usage of combination biologic therapy with etanercept and tocilizumab in two patients with moderately severe rheumatoid arthritis who failed etanercept therapy. This is the first report of combination anti-tumour necrosis factor and anti-interleukin 6 cytokine therapy in the treatment of rheumatoid arthritis.

Keywords: Rheumatoid arthritis; Combination biologic therapy; Etanercept; Tocilizumab

Introduction

Rheumatoid arthritis (RA) is a complex chronic autoimmune arthritis where many cytokines and chemokines including Tumour Necrosis Factor (TNF), and Interleukin-6 (IL-6) play important roles in the pathophysiology of RA. Studies have demonstrated the efficacy of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biological DMARDs, and their combination in RA treatment [1]. Patients with early RA started on combined therapy of csDMARDs with bDMARDs showed earlier clinical improvement and less joint damage. Etanercept (Enbrel) is a TNF receptor blocker with good efficacy in the treatment of RA. As shown in the TEMPO and COMET study, ACR 20 responses for the etanercept + methotrexate (MTX) group vs MTX alone were 49% vs 14% respectively at Week 2, and 86% vs 61%, respectively at Year 2 [2,3]. Yet 50% of patients did not achieve DAS28 remission while on etanercept + MTX!

Studies have shown that IL-6 and soluble IL-6 receptor (sIL-6R) levels are elevated in RA. Tocilizumab (Actemra) is a humanized monoclonal antibody that targets the IL-6 receptor [4]. Tocilizumab binds to soluble and membrane-bound IL-6 receptors and inhibits IL-6 signaling. This leads to reduction of acute phase reactants, reduced B-cell activation and inhibits differentiation of T-helper cells into inflammatory Th17 cells. Tocilizumab (Actemra), which is effective as a monotherapy or combination therapy with methotrexate (MTX) for the treatment of RA, has also been shown to be have some efficacy in anti-TNF

therapy inadequate response (IR) RA patients in the RADIATE trial. 50% of patients achieved ACR20 response at week 24, but only 20% achieved ACR50 response [5]. In the SUMMACTA trial, it was shown that the intravenous (IV) form given at 8mg/kg and the subcutaneous form (s/c) of tocilizumab given at 162mg weekly had similar efficacy in DMARD IR patients with moderate to severe RA. 73% and 69% of patients achieved ACR20 responses at week 24 respectively [6]. So 50% of anti-TNF IR RA patients did not achieve any response even with tocilizumab. This is the first report of the successful usage of combination biologic therapy with etanercept and tocilizumab for the treatment of 2 patients with active RA who had relapsing disease despite anti-TNF monotherapy.

Case report 1

The first case is a 47-year-old, German lady who was diagnosed with RA in March 2016 after presenting with symmetrical polyarthritis for 3 months affecting the shoulders, knees and hands. Blood tests showed elevated ESR, C-reactive protein and positive RA factor and anti-CCP. She was started on s/c etanercept 25mg/week and prednisolone and methotrexate (MTX). She became intolerant to both prednisolone and MTX and both were stopped. Other DMARDs including cyclosporine A, leflunomide and mycophenolate were tried but she developed adverse reactions and decided to have etanercept monotherapy 25mg every week. She was initially doing well but after a few months had intermittent flares. In Jan'17 had a moderate-severe

flare which required intravenous (IV) methyl prednisolone. Her etanercept was increased to 50mg/week. Her RA stabilized for 3 months. By April'17, she had recurrent flares and by day 5 post etanercept injection, her joint pains would recur. She was switched to twice weekly etanercept 25mg injection every Tuesday and Friday. She was in remission until June'17 when she had another flare requiring IV methylprednisolone. She was tried on a combination biologic therapy of s/c etanercept 25mg and s/c tocilizumab (Actemra) 162mg once a week. Her RA improved with ACR70 response the following week and by the 4th week, she was 90% better. The CPR normalized from 6.6mg/dl to 0.7mg/dl.

Case Report 2

CKP is a 65 year old Chinese man, with severe RA factor positive, anti-CCP positive RA diagnosed in January 2017. He was initially started on MTX by another rheumatologist but stopped because of liver dysfunction. He saw me 2 weeks later and I started him on s/c etanercept (Enbrel) 25mg/wk, cyclosporine A and prednisolone. He improved for the first 3 months, and then began to have active synovitis of the ankle joints in March 2017. The S/C Enbrel was increased to 50mg. He still had active disease with severe polyarticular flares. RA factor increased from 524IU/mL to 1246IU/mL and C - reactive protein (CRP) from 69.3mg/L to 93.4mg/L. He was started on IV biosimilar infliximab (Remsima) 200mg induction dose in June 2017 with improvement in the joint synovitis and pain. After the 2nd dose of IV Remsima, he developed rashes, likely to be allergy to Remsima. Hence the 3rd injection dose was not given. He continued on daily prednisolone 5mg bid and celecoxib 200mg bid. He developed recurrent joint pain and morning stiffness of 2 hours duration with left wrist and ankle synovitis. ESR was 101mm/hr, CRP increased to 104.9mg/L and RAF level increased to 1,981IU/mL. He was started on combination biologic DMARD with s/c Etanercept 25mg and s/c Actemra 162mg in July 2017. He was given a total of 6 combination s/c Etanercept and Actemra injections over the next 2 months. His RA symptoms improved and he was able to discontinue celecoxib with 20% reduction of RAF to 1632IU/mL and ESR to 84mm/hr.

Discussion

Combination biologic therapy was first proposed by Isaac et al in 1999 where combination therapy is designed to achieve additive or synergistic effects by targeting different effector mechanisms or cell activation pathways [7]. In this first report, TNF inhibitor was combined with Anti-CD4 monoclonal antibody. This was an open study of 9 patients with multi-DMARD resistant RA. There was some evidence of short term synergy with the 2 agents, and 3 patients had long term minimal disease activity for at least 1 year after only 3 months of therapy. There are few reports on the usage of combination bDMARDs in RA. Combination bDMARDs may have superior efficacy in the treatment of arthritis and may overcome the limited therapeutic responses obtained with single cytokine neutralization [1].

Safety of rituximab (RTX) in combination with other bDMARDs (ADA, ETN, AVT or IFX) in RA was reported as an open-label study [8]. Rigby and colleagues showed that no serious adverse events occurred within 24 h of any RTX infusion, and that efficacy improved at week 48 compared with that at week 24. Bispecific antibodies against TNF and interleukin (IL)-17 have been reported to be more effective than single blockade in a model of arthritis in mice [9]. Combination therapy using ETN plus ANK was reported to provide no additional benefit but there was an increased risk of infection compared with ETN monotherapy, so was not recommended for RA treatment [10].

In the setting of psoriatic arthritis, there are 2 case reports of the successful usage of combination biologic treatment with anti-TNF inhibitor (1 with etanercept and 1 with adalimumab) and ustekinumab (an anti-IL12/23 inhibitor) [11,12]. This is the first report of the successful usage of combination anti-TNF and anti-IL-6 biologic DMARD therapy for the treatment of moderately-severe RA in the setting of anti-TNF failure. And this case reports illustrate that the concept that the use of combination biologic therapy to achieve additive or synergistic effects by targeting different effector mechanisms (in this case the TNF and IL-6 cytokines) or cell activation pathways in the complex pathogenetic mechanisms of RA may be needed to bring difficult to treat RA patients under disease control or remission. Further studies are needed in more patients and on a longer term basis to ascertain the efficacy, sustainability, safety and cost-effectiveness of such combination biologic therapy. As rheumatologist faced with patients who have relapsing disease and drug resistant RA, combination biologic DMARDs may represent one of the novelties in the treatment of rheumatoid arthritis in the future [13].

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References

1. Kentaro I, Tatsuya K (2016) Combination therapy with biologic agents in rheumatic diseases: current and future prospects. *Ther Adv Musculoskelet Dis* 8(5): 192-202.
2. Klareskog L, vander Heijde D, de Jager JP, Gough A, Kalden J, et al. (2004) Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 363(9410): 675-681.
3. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, et al. (2008) Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 372(9636): 375-382.
4. Navarro-Millán I, Singh JA, Curtis JR (2012) Systematic review of tocilizumab for rheumatoid arthritis: a new biologic agent targeting the interleukin-6 receptor. *Clin Ther* 34(4): 788-802.
5. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, et al. (2008) IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre

- randomised placebo-controlled trial. *Ann Rheum Dis* 67(11): 1516-1523.
6. Burmester GR, Rubbert-Roth A, Cantagrel A, Hall S, Leszczynski P, et al. (2014) A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). *Ann Rheum Dis* 73(1): 69-74.
 7. Isaacs JD, Morgan AW, Strand V (1999) Combination biologic therapy. *Clin Exp Rheumatol* 17(6 Suppl 18) S121-S124.
 8. Rigby W, Mease P, Olech E, Ashby M, Tole S (2013) Safety of rituximab in combination with other biologic disease-modifying antirheumatic drugs in rheumatoid arthritis: an open-label study. *J Rheumatol* 40(5): 599-604.
 9. Fischer JA, Hueber A, Wilson S, Galm M, Baum W, et al. (2015) Combined inhibition of tumor necrosis factor α and interleukin-17 as a therapeutic opportunity in rheumatoid arthritis: development and characterization of a novel bispecific antibody. *Arthritis Rheumatol* 67(1): 51-62.
 10. Genovese M, Cohen S, Moreland L, Lium D, Robbins S, et al. (2004) Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 50(5): 1412-1419.
 11. Babalola O, Lakdawala N, Strober BE (2015) Combined biologic therapy for the treatment of psoriasis and psoriatic arthritis: A case report. *JAAD Case Rep* 1(1): 3-4.
 12. Torre KM, Payette MJ (2017) Combination biologic therapy for the treatment of severe palmoplantar pustulosis. *JAAD Case Rep* 3(3): 240-242.
 13. Ferro F, Elefante E, Luciano N, Talarico R, Todoerti M (2017) One year in review 2017: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 35(5): 721-734.



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