

Tapering of TNF- α Inhibitors is Feasible for Rheumatoid Arthritis Patients who have Achieved Remission

Der-Yuan Chen^{1,2,3,4*}

¹Department of Medical Education and Research, Taichung Veterans General Hospital, Taichung, Taiwan

²Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung, Taiwan

³Faculty of Medicine, National Yang Ming University, Taipei, Taiwan

⁴Institute of Biomedical Science and Rong Hsing Research Center for Translational Medicine, National Chung Hsing University, Taichung, Taiwan

*Corresponding author: Dr. Der-Yuan Chen, Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung, No. 1650, Sec. 4, Taiwan Boulevard, Taichung 40705, Taiwan, Tel: +886-4-23593354; E-mail:

Received date: February 19, 2016; Accepted date: March 01, 2016; Published date: March 05, 2016

Copyright: © 2016 Chen DY. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Short communication

Considering the dose-dependent adverse effects and economic burdens of tumor necrosis factor (TNF)- α inhibitors [1,2], the feasibility of their tapering, either dose reduction or injection spacing, after achievement of remission for rheumatoid arthritis (RA) patients should be evaluated. Smolen et al. demonstrated that moderately active RA patients could more effectively maintain low disease activity under reduced dosage of etanercept than total withdrawal [3]. Emery et al. also revealed that tapering of TNF- α inhibitors for early RA patients who were in remission resulted in better disease control than withdrawal of biologics [4]. Although the relapses of disease activity is more common in RA patients who received tapering of TNF- α inhibitors compared with those under continuously full dosage of biologics [5-7], there was no significant difference in radiographic or functional outcome [6,7]. Besides, the meta-analysis [8] and 2015 recommendations [9] also suggested that continuing biologic therapy at a reduced dose for RA patients who have achieved remission allows for the fair to good outcomes to be sustained. However, there has been no well-established down-titration strategy for biologic treatment in RA patients.

Clinically it is also important to search for predictive markers, which could identify patients who may maintain good outcome after down-titration of TNF- α inhibitors. Haschka et al., in the Reduction of Therapy in patients with Rheumatoid arthritis in ongoing remission (RETRO) study, revealed the presence of anticitrullinated protein antibodies (ACPA) was associated with disease relapses when biologics were tapered [5]. Using the same cohort, multi-biomarker disease activity (MBDA) score could improve the prediction of disease relapses in RA patients undergoing tapering of disease-modifying anti-rheumatic drugs after achieving remission [10]. In spite of the conflicting results regarding the value of serum drug trough levels for predicting successful dose reduction [11,12], drug level monitoring may help clinicians optimize anti-TNF- α therapy and prevent overtreatment for RA patients in clinical practice [11,13,14]. Recently, Naredo et al. demonstrated that the presence of Doppler ultrasound-detected synovitis may

predict for failure of biologic tapering for RA patients in sustained clinical remission [15]. In addition, a disease activity-guided dose-reducing strategy of TNF- α inhibitors for treating RA patients is non-inferior to usual care in terms of major flares, and the implementation of such strategy would improve the cost-effectiveness of biologic therapy [6].

In conclusion, based on the findings of previous studies, the meta-analysis, and the current treatment guidelines, tapering of TNF- α inhibitors is feasible for RA patients in sustained remission [3-9]. Further studies in search for reliable markers to predict for successful tapering of TNF- α inhibitors in such RA patients are warranted.

References

1. Krieckaert CL, Nair SC, Nurmohamed MT, van Dongen CJ, Lems WF, et al. (2015) Personalized treatment using serum drug levels of adalimumab in patients with rheumatoid arthritis: an evaluation of costs and effects. *Ann Rheum Dis* 74: 361-368.
2. Isvy A, Meunier M, Gobeaux-Chenevier C, Maury E, Wipff J, et al. (2012) Safety of rituximab in rheumatoid arthritis: a long-term prospective single-center study of gammaglobulin concentrations and infections. *Joint Bone Spine* 79:365-369.
3. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, et al. (2013) Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 381:918-929.
4. Emery P, Hammoudeh M, FitzGerald O, Combe B, Martin-Mola E, et al. (2014) Sustained remission with etanercept tapering in early rheumatoid arthritis. *N Engl J Med* 371: 1781-1792.
5. Haschka J, Englbrecht M, Hueber A, Manger B, Kleyer A, et al. (2016) Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: interim results from the prospective randomized controlled RETRO study. *Ann Rheum Dis* 75:45-51.
6. van Herwaarden N, van der Maas A, Minten MJM, van den Hoogen FH, Kievit W, et al. (2015) Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomized controlled, non-inferiority trial. *BMJ* 350:h1389.

7. Fautrel B, Pham T, Alfaiate T, Gandjbakhch F, Foltz V, et al. (2016) Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicenter non-inferiority randomized open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid Arthritis Study). *Ann Rheum Dis* 75: 59-67.
8. van Herwaarden N, den Broeder AA, Jacobs W, van der Maas A, Bijlsma JW, et al. (2014) Down-titration and discontinuation strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity (Review). *Cochrane Database Syst Rev* 9:CD010455.
9. Singh JA, Saag KG, Bridges Jr. SL, Akl EA, Bannuru RR, et al. (2016) ACR 2015 recommendation for established rheumatoid arthritis. *Arthritis Rheumatol* 68: 1-26.
10. Rech J, Hueber AJ, Finzel S, Englbrecht M, Haschka J, et al. (2016) Prediction of disease relapses by multibiomarker disease activity and autoantibody status in patients with rheumatoid arthritis on tapering DMARD treatment. *Ann Rheum Dis* [Epub ahead of print]
11. Chen DY, Chen YM, Hsieh TY, Hung WT, Hsieh CW, et al. (2016) Drug trough levels predict therapeutic responses to dose reduction of adalimumab for rheumatoid arthritis patients during 24 weeks of follow-up. *Rheumatology (Oxford)* 55:143-148.
12. van Herwaarden N, Bouman CAM, van der Maas A, van Vollenhoven RF, Bijlsma JW, et al. (2015) Adalimumab and etanercept serum (anti)drug levels are not predictive for successful dose reduction or discontinuation in rheumatoid arthritis. *Ann Rheum Dis* 74:2260-1.
13. Pouw MF, Krieckaert CL, Nurmohamed MT, van der Kleij D, Aarden L, et al. (2015) Key findings towards optimising adalimumab treatment: the concentration-effect curve. *Ann Rheum Dis* 74: 513-518.
14. Sanmarti R, Inciarte-Mundo J, Estrada-Alarcon P, Garcia-Manrique M, Narvaez J, et al. (2015) Towards optimal cut-off trough levels of adalimumab and etanercept for a good therapeutic response in rheumatoid arthritis, Results of the INMUNOREMAR study. *Ann Rheum Dis* 74: e42.
15. Naredo E, Valor L, De la Torre I, Montoro M, Bello N, et al. (2015) Predictive value of Doppler ultrasound-detected synovitis in relation to failed tapering of biologic therapy in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 54:1408-1414.