Rheumatol Ther (2022) 9:305–307
https://doi.org/10.1007/s40744-021-00386-w

LETTER TO THE EDITOR

Considering Immuno-autonomics in Stratifying Successful Treatment of Rheumatoid Arthritis with Tumor Necrosis Factor Inhibition: Comment on Cohen et al. Rheumatol Ther 2021 June 19

Andrew J. Holman · Edward Keystone · Ernest Choy · Daniel Furst · Peter Taylor · Norman Gaylis

Received: August 6, 2021 / Accepted: October 12, 2021 / Published online: November 10, 2021

Keywords: Rheumatoid arthritis; Tumor necrosis factor inhibition; Immuno-autonomics; Heart rate variability

Cohen et al. have significantly advanced a solution to arguably the most pervasive conundrum in rheumatology: how to target specific immunosuppressive therapy most effectively [1]. In infectious disease and oncology, targeted therapy has been based upon pathogen susceptibility and tissue surface receptor expression, respectively. Predicting either positive or negative response to specific therapies in rheumatoid arthritis (RA) is certainly welcome and the molecular signature response classifier (MSRC) appears most promising and useful.

However, two issues come to mind after reviewing this important paper. First, disease activity has been a consistent predictor of poor tumor necrosis factor inhibition (TNFi), yet demographic characteristics were reported as 'not significantly different' among those responsive and those unresponsive to TNFi. This seems curious.

Second, there was mention of many studies attempting unsuccessfully to identify biomarkers or models unable to predict TNFi outcome in RA. We wish to bring to the authors' attention a 52-week, prospective, double-blind study of next-generation, high-fidelity heart rate variability (HRV) predicting TNFi outcome in RA and psoriatic arthritis [2]. Subjects with a poor autonomic nervous system (ANS) profile by the 'parasympathetic' measure (low) at day 0 achieved ACR (American College of Rheumatology) 20/50/70 outcomes of 40%/12%/0%, respectively. Subjects with a favorable ANS profile by the 'parasympathetic' measure (high)

This comment refers to the article available online at https://doi.org/10.1007/s40744-021-00330-y.

A. J. Holman (✉)
Pacific Rheumatology Associates, Inc PS, Seattle, WA, USA
e-mail: andrew.holman@inmedix.com

E. Keystone
Department of Medicine, Keystone Consulting Enterprises Inc, University of Toronto, Toronto, Canada

E. Choy
Division of Infection and Immunity, Arthritis Research UK CREATE Centre and Welsh Arthritis Research Network (WARN), Cardiff University School of Medicine, Cardiff, UK

D. Furst
University of California in Los Angeles Academy, Los Angeles, CA, USA

P. Taylor
Botnar Research Centre, University of Oxford, Oxford, UK

N. Gaylis
Arthritis and Rheumatic Disease Specialties, Aventura, FL, USA

achieved an ACR20/50/70 outcomes of 100%/88%/65%, respectively.

The receiver operating characteristic (ROC) area under the curve (AUC) for the MSRC was 0.64 for ACR50 at 26 weeks, with secondary outcomes reaching a ROC AUC of up to 0.74 among TNFi naïve subjects. The ROC AUC for 'parasympathetic' and sympathetic 'tension index' using next-generation, high-fidelity HRV for ACR50 at 26 weeks were 0.858 and 0.869, respectively [3]. Of note, the ROC AUC for ACR70 at 52 weeks were 0.926 and 0.918, respectively. In turn, this link between the regulatory power of the ANS driving immune function, i.e., immuno-autonomics, is hypothesized to be agnostic to the immunosuppressive chosen. Of course, additional rigorous studies will be required to confirm or refute that supposition.

Lately, immuno-autonomics and ANS optimization have become a target strategy to reduce RA burden [4]. The most prominent example is vagus nerve stimulation (VNS) to reactivate a dormant cholinergic anti-inflammatory reflex [5]. Implanted (cervical and splenic) as well as external (ear bud) VNS have been explored in RA.

ANS sympathetic stress activates proinflammatory cytokines and a host of other immune functions driving autoimmune diseases to excess [6]. We submit that targeting immunosuppressive choice in combination with optimizing ANS state may offer complimentary value. We look forward to a study where targeted TNFi selection is blended with immuno-autonomic intervention to enhance RA treatment outcomes. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

ACKNOWLEDGEMENTS

Funding. No Rapid Service Fee was received by the journal for the publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contribution. Text and review (all authors).

Disclosure. All authors are members of the Scientific Advisory Board for Inmedix, Inc. Dr. Holman is also co-founder, CEO, Board Director, and shareholder.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Cohen S, Wells AF, Curtis JR, Dhar R, Mellors T, Zhang L, Withers JB, Jones A, Ghiassian SD, Wang M, Connolly-Strong E, Rapisardo S, Gatalica Z, Pappas DA, Kremer JM, Saleh A, Akmaev VR. A molecular signature response classifier to predict inadequate response to tumor necrosis factor-α inhibitors: the NETWORK-004 prospective observational study.

Rheumatol Ther. 2021. https://doi.org/10.1007/s40744-021-00330-y.

2. Holman AJ, Ng E. Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis. Auton Neurosci. 2008;143(1–2):58–67. https://doi.org/10.1016/j.autneu.2008.05.005.

3. Holman AJ, Ng E. How substantive is heart rate variability as a predictor of anti-TNF treatment outcome for inflammatory arthritis? Arthritis Rheumatol. 2015;67(suppl 10):1571.

4. Taylor PC, Holman AJ. Rheumatoid arthritis and the emergence of immuno-autonomics. Rheumatology (Oxford). 2019;58(12):2079–80. https://doi.org/10.1093/rheumatology/kez216.

5. Tracey KJ. The inflammatory reflex. Nature. 2002;420:853–9.

6. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve—an integrative interface between two super systems: the brain and the immune system. Pharmacol Rev. 2000;52:595–638.