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Bench to Bedside – and Back Again: Finding the Goldilocks Zone within the Scleroderma Universe

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Systemic sclerosis (SSc) is a complex inflammatory connective tissue disease characterized by skin thickening, organ fibrosis and vasculopathy [1, 2]. The underlying disease mechanisms and pathophysiology are not fully understood. However, it appears to be, at least in part, driven by autoimmunity and inflammation associated with microvascular dysfunction ultimately resulting in excess extracellular matrix deposition in target organs [2-4]. Clinical heterogeneity coupled with our lack of understanding of the disease pathogenesis means that current treatment strategies are mostly organ based therapies using anti-rheumatic drugs that were originally approved for other indications [5]. Of course, this clinical diversity not only provides challenges to discovery of disease mechanisms, it also complicates often underpowered clinical trials that aim to find the right drugs for the right patient at the right time.

One approach towards discovery of the "Goldilocks Zone" of disease modifying therapy for all patients with SSc is starting at a point of known commonality. For example, SSc is often characterized by the presence of autoantibodies [6, 7]. More specifically, there have been recent interest in B-cell biology and modulation, including data derived from animal models of disease, human tissue analyses and even small randomized clinical trials of B-cell depletion in patients with SSc [6, 8, 9]. In addition to their role in autoantibody formation, B-cells have been shown to be elevated in blood and tissue samples of patients with SSc, with abnormal chronic activation while demonstrating secretion of important disease cytokines such as IL-6 and TGF-β [6].

In this issue of Arthritis and Rheumatology, Gordon et al present their experience with belimumab in a randomized placebo controlled trial. Belimumab is a human monoclonal antibody directed against B-cell Activating Factor (BAFF), also known as B-lymphocyte Stimulator (BLyS). This study assessed the potential benefit of adding belimumab to standard treatment of early diffuse cutaneous SSc (dcSSc) with mycophenolate mofetil (MMF). The authors evaluated safety and looked for signals of efficacy. The results show improvement in modified Rodnan skin score (MRSS) during the treatment period with a numerically greater fall in those patients randomized to receive belimumab (MRSS -10 vs. -3), albeit statistically non-significant. Interestingly, the authors investigated differential gene expression for patients who

received belimumab, which clearly identified the clinical improvers compared to non-responders.

While the trends toward benefit for use of belimumab are promising for patients with SSc, this modern study design also highlights an important innovative paradigm shift in research approach of heterogeneous autoimmune connective tissue diseases. Specifically, in this study, the research design incorporated clinical data along with differential gene expression data, which allow for a deeper, more intelligent interpretation of the end-point results. Although the study was underpowered to show statistical significance for overall clinical outcomes, we are encouraged by the biological data that demonstrates expected drug target modulation along with identification of a subset of patients who derived substantial benefit. This is important since one can envision a truly translational research loop that not only allows bench data to drive clinical trials, but also clinical trial experiences to guide further biological research.

Therefore, another approach towards discovery of our elusive Goldilocks Zone may be translating traditional clinical trials data into modern basic and clinical research that unravels the heterogeneity of SSc. Studies from Milano et al [10] and others [11] have shown, using novel techniques, that disease stratification and personalization is within reach. Going forward, biological precision will allow clinicians and researchers to reveal more powerful truths within small trials of uncommon and rare diseases. For instance, a very small study of Imatinib in active diffuse cutaneous systemic sclerosis used cytokine changes from skin biopsies and serum to determine if there were changes correlating with treatment response [12].

SSc trial design should take into consideration various factors such as background immune suppression in all groups vs. not including ethics of GCP vs. gaining insight into how a treatment works, interpretation of pilot studies in general, use of genomics or other parameters to help to understand early trial results) and overall interpretation of pathophysiology of early SSc and role of B cell signalling.

The strengths of the current study include randomization, blinding, a placebo control and the addition of study drug to a standardized background treatment (MMF). Limitations include the small patient number, single center design with potential bias, or center effect, and the confounding effect of concurrent immunosuppression with mycophenolate mofetil (MMF).

This co-therapy makes it impossible to attribute any treatment effect solely to belimumab and may have blunted the difference in treatment response between the two groups. However, it allowed for all patients to receive standard of care which enhances recruitment and allows for good clinical practice. Future studies may need to determine if MMF is needed and also if other immune suppressive drugs could be used. This study provides data for a power calculation of a larger trial.

The gene expression analysis may be difficult to interpret due to small numbers and there may be the MMF response and natural history confounding the belimumab effect. However, they showed modulation of B cell receptor activation and pro-fibrotic signaling in the belimumab arm and not in clinical improvers in the placebo group.

In conclusion, novel early-stage trial designs that incorporate standard of care treatment and biomarkers to understand response such as gene expression within a randomized trial may be considered a template for future SSc trials.

References

1. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med. 2009 May 7;360(19):1989-2003.
2. Denton CP, Black CM, Abraham DJ. Mechanisms and consequences of fibrosis in systemic sclerosis. Nat Clin Pract Rheum. 2006 Mar;2(3):134-44.
3. Bhattacharyya S, Wei J, Tourtellotte WG, Hinchcliff M, Gottardi CG, Varga J. Fibrosis in systemic sclerosis: common and unique pathobiology. Fibrogenesis & tissue repair. 2012;5(Suppl 1):S18.
4. Beyer C, Schett G, Distler O, Distler JH. Animal models of systemic sclerosis: prospects and limitations. Arthritis Rheum. 2010 Oct;62(10):2831-44.
5. Lee JJ, Pope JE. Diagnosis and Management of Systemic Sclerosis: A Practical Approach. Drugs. 2015 Dec 10.
6. Sato S, Fujimoto M, Hasegawa M, Takehara K, Tedder TF. Altered B lymphocyte function induces systemic autoimmunity in systemic sclerosis. Molecular Immunology. 2004 2004/11/01/;41(12):1123-33.
7. Bhattacharyya S, Wei J, Varga J. Understanding fibrosis in systemic sclerosis: shifting paradigms, emerging opportunities. Nat Rev Rheumatol. 2012 Jan;8(1):42-54.
8. Daoussis D, Melissaropoulos K, Sakellaropoulos G, Antonopoulos I, Markatseli TE, Simopoulou T, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. Seminars in Arthritis and Rheumatism. 2017 2017/04/01/;46(5):625-31.
9. Leask A. Emerging targets for the treatment of scleroderma. Expert opinion on emerging drugs. 2012 Jun;17(2):173-9.
10. Milano A, Pendergrass SA, Sargent JL, George LK, McCalmont TH, Connolly MK, et al. Molecular subsets in the gene expression signatures of scleroderma skin. PloS one. 2008;3(7):e2696.

11. Derrett-Smith EC, Martyanov V, Chighizola CB, Moinzadeh P, Campochiaro C, Khan K, et al. Limited cutaneous systemic sclerosis skin demonstrates distinct molecular subsets separated by a cardiovascular development gene expression signature. Arthritis Res Ther. 2017 Jul 04;19(1):156.
12. Pope J, Walker KM, de Leon F, Vanderhoek L, Seney S, Summers KL. Correlations between changes in cytokines and clinical outcomes for early phase (proof of concept) trials in active diffuse systemic sclerosis using data from an imatinib study. Rheumatology (Oxford). 2014 Oct;53(10):1830-4.