Treatment Targeting Type I Interferon Pathways in Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by several autoantibodies against nucleic acid and significant production of interferon (IFN), particularly IFN-α. Most of the patients with SLE demonstrate increased production of type I IFN related to an over-expression of type I IFN-regulated genes known as IFN signature (1). Therefore, targeting IFN could be an emerging strategy for developing novel therapies for SLE.

Recent studies aimed to inhibit IFN pathway have shown clinical efficacy. Based on this, several clinical trials of type I IFN antagonists have been underwent and reached phase 3. In 2016, rontalizumab, a humanized IgG1 monoclonal antibody against IFN-α, was evaluated in patients with moderate-to-severe active SLE (2). The efficacy response rates were not met and the further trial was discontinued. Sifalimumab, a fully human IgG1 monoclonal antibody, was assessed in patients with moderate-to-severe active SLE in addition to standard-of-care (SOC) medications (3). The proportion of patients who archived the response was significantly higher in the treatment groups compared to placebo. However, the effect sizes were small and Herpes zoster infections were more frequent with sifalimumab. Based on these limitations, sifalimumab would not enter next stage of development.

Recently breakthrough study in 2017 showed the promising results. Anifrolumab, an anti-IFN-α receptor monoclonal antibody, was assessed in patients with moderate-to-severe active SLE, excluding active and severe lupus nephritis or neuropsychiatric SLE (4). In this study, anifrolumab in addition to SOC treatment reduced disease activity compared to placebo, particularly patients with a high IFN signature.

Currently, anifrolumab is evaluated as a potential treatment of SLE in two phase 3 studies. In future, personalized characterization of IFN pathway may provide guidance for selection of tailored treatment in patients with SLE.

To conclude, Most of patients with SLE demonstrate increased production of type I IFN particularly IFN-α which related to an over-expression of type I IFN-regulated genes as know as IFN signature. Anifrolumab in addition to SOC treatment reduced disease activities compared to placebo in patents with moderate-to-severe active SLE, particularly patients with a high IFN signature.

References

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