patients. This can be done by integrating clinical phenotype with genetic setup, gene expression profile and analysis of activated pro inflammatory pathways.

**19 CLINICAL TRIALS WITH IFN BLOCKERS**

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Background Type I interferon (IFN) pathway activation has long been demonstrated in patients with systemic lupus erythematosus (SLE). The target of drug development in SLE, approaches to inhibit type I IFN have been quite eclectic. The initial strategy, which utilized a monoclonal antibody to interferon-alpha, was not successful as the phase 2 study in SLE with rontalizumab failed to achieve the primary end point of the study. Shortly thereafter, the results of a phase 2 SLE study with sifalimumab, a second monoclonal antibody to interferon-alpha, were released. While benefit was achieved, the pharmacodynamic and clinical effects were not as robust as those attained in a phase 2 SLE study with anifrolumab, an antibody to the type I IFN receptor that inhibits all type I IFNs. The phase 3 anifrolumab program was comprised of two studies, known as TULIP 1 and TULIP 2. TULIP 1 evaluated two doses (150 and 300 mg) administered intravenously every 4 weeks through week 48 with the primary end point, SLE Responder Index response rate, at week 52. Although this study failed to achieve the primary end point, it was recognized after unblinding that 8% of study subjects were misclassified as non-responders because of NSAID use. While post-hoc revisions to the restricted medication rules did not change the primary outcome of TULIP 1, these modifications did result in several successful secondary outcomes, including the British Isles Lupus Assessment Group–based Composite Lupus Assessment response rates (BICLA: placebo [29.6%] vs anifrolumab 300 mg [46.1%]). An additional outcome of the post-hoc evaluation of TULIP 1 was the modification to the TULIP 2 primary end point.

TULIP 2’s initial design was identical to TULIP 1 with the exception that just one dose of anifrolumab (300 mg) was compared to placebo. However, before unblinding, the end point was switched from SRI at week 52 to BICLA response rate at week 52. TULIP 2 not only achieved the primary outcome (BICLA: placebo [31.5%] vs anifrolumab 300 mg [47.8%]), but multiple secondary end points were also attained, chief of which were the ability to taper corticosteroids as well as improvement of cutaneous disease activity. Safety signals of note included a higher rate of herpes zoster reactivation (placebo: 1.1% vs anifrolumab: 7.2%).

While not as advanced in development, there are several other programs that are targeting the IFN pathway. RSLV-132 is an RNase-Fc fusion protein that enzymatically degrades circulating RNA, thus inhibiting its ability to bind to toll-like receptors (TLR) and activate plasmacytoid dendritic cells. Direct inhibition of TLRs is yet another strategy being employed to target the innate immune system. Immunization with an IFN-alpha-KLH conjugate allows the host to produce his or her own antibodies to IFN-alpha. Plasmacytoid dendritic cells (pDC) are the major producers of type I IFN, and thus they represent a principal target for SLE drug development. BIIB059 is a monoclonal antibody that binds BDCA2, a protein uniquely expressed on pDCs. When BDCA2 is ligated with BIIB059, the protein is internalized, and production of cytokines, chemokines, and interferons is inhibited. In late 2019, it was announced that two phase 2 studies that evaluated cutaneous lupus as well as SLE achieved their respective end points. Baricitinib, an inhibitor of JAK1 and JAK2, achieved success in a phase 2 SLE study and is currently in phase 3. Let’s not forget hydroxychloroquine, which suppresses TLR activation through its inhibition of endosomal acidification.

The future is bright for patients with SLE as research is providing greater insights into SLE pathogenesis that are being translated to drug discovery.