

Anifrolumab: An Inhibitor of Type I Interferon for the Treatment of Patients with Systemic Lupus Erythematosus

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Anifrolumab is the only US Food and Drug Administration-approved therapy for patients with systemic lupus erythematosus (SLE) that directly targets type I interferons (IFNs). The phase I study in scleroderma and phase II study in SLE served as a foundation for the phase III programme that included the TULIP-1 and TULIP-2 SLE trials. We review the biology of IFNs and the scientific rationale for developing an inhibitor of the type I IFN pathway. The focus then turns to the specific trials that led to regulatory approvals.

Keywords

Anifrolumab, systemic lupus erythematosus (SLE), type I interferon, anti-interferon therapy, MEDI-546

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Isaacs and Lindenmann first identified interferons (IFNs) in 1957.¹ They discovered that chicken embryo chorioallantois membranes pre-treated with heat-inactivated influenza virus inhibited the growth of live influenza virus, and thus, the abridged term for 'viral interference' became 'interferon'. A little over 20 years later, there was speculation that not only did IFNs offer protection against viral infections, they appeared to contribute to the immunologic disturbances present in autoimmune diseases. This was based on research performed at the National Institutes of Health where Hooks et al. assayed IFN levels in the blood of patients with a variety of autoimmune conditions.² The patient subgroup with the highest frequency (70%) of detectable IFNs consisted of those with active systemic lupus erythematosus (SLE), an observation that has since held true.

Rönblom et al. first described a patient being treated for a malignancy with IFN- α who developed a lupus-like illness in 1990.³ While evidence was accumulating linking IFNs to SLE pathogenesis, translational research was hampered by difficulty in assaying IFNs in blood samples. However, in 2003, a major technologic advance occurred – the IFN gene signature (IFNGS) was introduced, and it accelerated translational research in this area.^{4,5} While IFN levels could not be easily measured, evidence of IFN pathway activation could now be identified with the new gene microarray technology. In recent years, a sensitive assay for measuring IFN- α has been introduced.⁶

There are three types of IFNs: type I, II and III. Type I IFNs consist of five subtypes: α , β , ω , ϵ , and κ . Type II IFNs are γ IFNs, and type III, λ IFNs. All five subtypes of type I IFNs bind the same receptor, the IFN- α receptor (IFNAR), whereas IFN- γ binds a distinct receptor, as does IFN- λ . IFNGS were identified in patients with SLE, especially those with clinical and serologic activity.⁷ Type I IFNs are broadly pro-inflammatory, and although they are a component of the innate immune system, their effects extend to the adaptive immune system as well.⁷ With the role of IFN in the pathogenesis of SLE becoming more evident, the question was whether IFN inhibitors could be incorporated into a treatment strategy.

In the early 2000s, the limited research into SLE drug development was focused on targeting B and T cells.^{8–11} Sifalimumab and rontalizumab were antibodies to IFN- α that were developed for the treatment of SLE. However, rontalizumab failed in a phase II SLE trial.¹² While sifalimumab produced modest results in the phase II SLE trial, there was a better strategy looming.¹³ It was theorized that by blocking the type I IFN receptor, as opposed to inhibiting just one of the five type I IFN subtypes, type I IFN would be inhibited to a greater extent.¹³ Anifrolumab is an immunoglobulin (Ig) G monoclonal antibody that binds to subunit 1 of IFNAR and blocks binding to the receptor by all type I IFN subtypes. As such, much greater IFN inhibition was observed with anifrolumab compared with sifalimumab.¹⁴ Given this biology, the true test was to determine whether anifrolumab would be more clinically effective than antibodies that target IFN- α only.

Clinical development

Phase I study

The phase I trial of anifrolumab was not conducted in patients with SLE; rather, the study was performed in patients with scleroderma, a disease also associated with IFNGS. In this study, safety, pharmacokinetics (PK), immunogenicity and pharmacodynamics of intravenous (IV) anifrolumab (known at the time as MEDI-546) were evaluated.¹⁵ Inhibition of the type I IFNGS was observed, with adequate safety, so the programme advanced to phase II, which was performed in patients with SLE.

Phase II study (MUSE)

Sifalimumab and rontalizumab, monoclonal antibodies to IFN- α , advanced to phase II in SLE. Rontalizumab met neither the primary nor secondary efficacy endpoints, and thus, development was discontinued.¹² On the other hand, sifalimumab at the highest dose of 1,200 mg every 4 weeks achieved a statistically significant effect size of approximately 14%, compared with placebo.¹³

Theorizing that greater inhibition of IFNGS by anifrolumab would yield superior clinical results in SLE compared with sifalimumab, the phase II randomized study to evaluate the efficacy and safety of MEDI-546 in subjects with systemic lupus erythematosus (MUSE; A Study of the Efficacy and Safety of MEDI-546 in Systemic Lupus Erythematosus, ClinicalTrials.gov identifier: NCT01438489) clinical trial was launched.¹⁶ In this phase IIb, randomized, double-blind, placebo-controlled study of adults with moderate-to-severe SLE, there were three treatment arms: placebo, anifrolumab 300 mg and anifrolumab 1,000 mg, all added to a background of standard-of-care treatment. Infusions were administered every 4 weeks. Entry required a screening SLE Disease Activity Index 2000 (SLEDAI) of 6 or greater (and a clinical SLEDAI ≥ 4 at baseline), a British Isles Lupus Assessment Group index (BILAG) score of one A or two Bs, physician global assessment ≥ 1 , serologic activity (antinuclear antibodies, DNA or Smith antibodies), and treatment with at least one SLE medication. These activity requirements were more stringent than studies performed during that era. Stratification factors at randomization included SLEDAI < 10 versus ≥ 10 , prednisone dosage < 10 versus ≥ 10 mg/day, and high versus low type I IFNGS based on a four-gene expression assay. The primary endpoint comprised the SLE Responder Index (SRI[4]) score at day 169 and a sustained reduction of oral corticosteroids to < 10 mg/day of prednisone beginning at day 85 and maintained through day 169. A key secondary endpoint was the proportion of patients who achieved response defined by SRI(4) at day 365 and who also tapered prednisone to < 10 mg/day from week 40 through week 52.¹⁶

For the primary endpoint, the group randomized to 300 mg of anifrolumab every 4 weeks responded with an effect size of nearly 17% as compared with the placebo (odds ratio: 2.38; $p=0.014$); at 1 year, the effect size increased to 26%.

Interestingly, greater benefit was observed with the 300 mg dose compared with the 1,000 mg dose. Improvement was observed in cutaneous disease using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), arthritis activity, BILAG-based combined lupus assessment (BICLA), as well other metrics. Herpes zoster reactivation occurred in 2%, 5% and 9% of patients treated with placebo, 300 mg anifrolumab and 1,000 mg anifrolumab, respectively. IFNGS inhibition in both treatment arms was approximately 90% compared with pre-treatment values.¹⁶ This highly successful phase II study served as a foundation for the phase III programme, which consisted of the Treatment of uncontrolled lupus via the interferon pathway (TULIP) studies, TULIP-1 (Efficacy and Safety of Two Doses of Anifrolumab Compared to

Placebo in Adult Subjects With Active Systemic Lupus Erythematosus; ClinicalTrials.gov identifier: NCT02446912) and TULIP-2 (Efficacy and Safety of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus; ClinicalTrials.gov identifier: NCT02446899).^{17,18}

Phase III studies (TULIP)

The TULIP trials were originally modelled on the MUSE study with a few modifications: 1) the endpoint, SRI(4), was evaluated at 1 year; 2) the steroid taper requirement was removed from the endpoint; 3) a 150 mg dose was added in TULIP-1; and 4) the 1,000 mg dose was omitted from further development.¹⁶⁻¹⁸ TULIP-1 had three arms, randomized 2:1:2, respectively: placebo, 150 mg of IV anifrolumab, and 300 mg of IV anifrolumab.¹⁷ TULIP-2 had two arms: placebo and 300 mg of IV anifrolumab.¹⁸ As in MUSE, anifrolumab was administered IV every 4 weeks, and patients were permitted to continue background standard-of-care medications as long as they met the protocols' medication rules. Stratification factors were identical to the MUSE study.

To the shock of the lupus community, TULIP-1 did not meet its primary endpoint.¹⁷ Contributing, in part, to the study's failure to achieve statistical significance of the primary endpoint was one of the medication rules, which classified patients as non-responders if they had taken a non-steroidal anti-inflammatory drug (NSAID) during the study. Approximately 8% of patients were classified as non-responders solely because of NSAID use during the study. An advisory group was convened to opine on the appropriateness of this particular medication rule. The committee concluded that non-responder classification because of NSAID use was clinically inappropriate.¹⁷ Despite a *post hoc* analysis with modified restricted medication rules, statistical significance was not attained with the original SRI(4) endpoint.¹⁷ This led to a review of all restricted medication responder classification rules, and after unblinding, SLE experts and the sponsor revised the restricted medication rules. NSAID use prior to week 50 no longer resulted in non-responder classification of SLE response. Despite applying the modified rule to the TULIP-1 data, statistical significance was still not achieved. Herpes zoster reactivation was once again observed with greater frequency in the anifrolumab-treated patients.

There were several key secondary endpoints that were successful in TULIP-1, including CLASI activity improvement, reduction in joint scores, steroid reduction and BICLA.¹⁷ In fact, the effect size for BICLA was approximately 16% in the 300 mg treatment group. Given the benefit of anifrolumab as measured by BICLA, the conundrum was whether the endpoint of the TULIP-2 trial should be modified since the data were still blinded. After much discussion among experts, the primary endpoint of TULIP-2 was changed from SRI(4) to BICLA.

Not only did TULIP-2 succeed in meeting the BICLA outcome with an effect size of approximately 16%, the effect size with SRI(4) was approximately 18%.¹⁸ This trial met several secondary endpoints, including BICLA response in those patients with high IFNGS expression at week 52, sustained steroid reduction and CLASI response at week 12. The joint count reduction at week 52 was not statistically significant.

The kinetics of response of anifrolumab in TULIP-2 demonstrated separation between anifrolumab and placebo within 2 months of initiating treatment. This rapid response was supported with CLASI, as well as an outcome measure that evaluated time to first BICLA response maintained through week 52.¹⁸

Conclusions and future study

Although the failure of TULIP-1 to achieve the SRI(4) endpoint created much uncertainty regarding the regulatory approvability of anifrolumab, the US Food and Drug Administration approved anifrolumab on 2 August 2021. It is indicated for the treatment of adult patients with moderate-to-severe SLE who are receiving standard therapy.¹⁹ The efficacy of anifrolumab has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus, and therefore is not recommended in these situations. Unlike belimumab, another common treatment for SLE, there is no requirement for autoantibody positivity. The recommended dosage is 300 mg as an IV infusion over a 30-minute period every 4 weeks.

Many questions still need to be answered. For example, why was there discordance in TULIP-1 between the SRI(4) and BICLA outcomes? We also need to understand the pathways that are active in patients who are

IFNGS low. Many topics have been or are being addressed using pooled data from TULIP-1 and -2. At the time of writing, four such articles have been published, which address safety, flares, the meaningfulness of BICLA response and the PK–efficacy relationship.^{20–23} The use of anifrolumab in patients with proliferative lupus nephritis has been studied in a phase II clinical trial (Safety and Efficacy of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Proliferative Lupus Nephritis [TULIP-LN1]; ClinicalTrials.gov identifier: NCT02547922)²⁴ and will be further evaluated in a phase III study (Efficacy and Safety of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus; ClinicalTrials.gov identifier: NCT02446912).^{17,24,25} Other rheumatic diseases, such as Sjögren’s syndrome, myositis and scleroderma, are associated with type I IFN pathway activation, and thus are appropriate conditions for further treatment studies with anifrolumab.²⁶ The approval of anifrolumab will no doubt open the door for more research and make for brighter futures for patients with SLE. □

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