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Type I interferon antagonists in clinical development for lupus

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a severe chronic and incurable autoimmune disease. Treatment includes glucocorticoids and small molecule immunosuppressants which typically result in partial responses, and hence there is a great need for new therapies. The type I interferon (IFN) pathway is activated in more than 50% of SLE patients, and it is strongly implicated as a pathogenic factor in SLE. A number of therapeutics have been developed to target type I IFN in SLE.

Areas Covered: We searched the literature using "SLE and interferon antagonists" as search terms. This identified a number of therapeutics that have entered clinical development targeting type I IFN in SLE. These include monoclonal antibodies against type I IFN cytokines and a kinoid vaccination strategy to induce anti-IFN antibodies. We discuss these in our article.

Expert Opinion: Type I IFN antagonists have had some success, but many molecules have not progressed to phase III. These varied results are likely attributed to the multiple concurrent cytokine abnormalities present in SLE, the imprecise nature of the IFN signature as a readout for type I IFN and difficulties with clinical trials such as background medication use and diffuse composite disease activity measures. Despite these challenges, it seems likely that a type I IFN antagonist will come to clinical utility for SLE given the large unmet need and the recent phase III success with anifrolumab.

Keywords

lupus; interferon; clinical trials; autoimmune disease; systemic lupus erythematosus; type I interferon pathway; IFN pathway; type I IFN antagonists

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune condition that is characterized by a broad range of symptoms, including rash, nephritis, arthritis, and central nervous system involvement [1]. A key characteristic of SLE is the presence of high titers of autoantibodies, which likely play a pathogenic role causing inflammation and tissue damage in affected organs [1]. High disease activity has been correlated with decreased quality of

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life, irreversible organ damage, and shortened life span. SLE results from a complex interplay of immunologic, genetic and environmental factors [2].

Significant advances in genetic association and biomarker studies have led to the identification of type I Interferons (IFNs) as a potential therapeutic target in SLE patients [3, 4]. IFNs were originally discovered in the 1950's as antiviral cytokines, since then many different IFNs have been described and grouped into three main families: type I, type II, and type III [5]. Type I IFNs are a family of homologous proteins including IFN-alpha (IFN-α) which has 13 subtypes, IFN-beta (IFN-β), IFN-kappa (IFN-κ), and IFN- omega (IFN-ω) [5]. Type I IFNs play a significant role in the innate and adaptive immunity response against viruses and bacteria and can be induced by ligation of toll-like receptors and cytosolic nucleic acid sensors [6–8]. Expression of the type I IFN genes is strictly regulated. For example, IFN-α is found in very low levels in healthy individuals outside the setting of active infection, making the persistent upregulation of IFN-α in SLE and some other autoimmune diseases highly notable, supporting a pathogenic role [8].

Type I IFN increases antigen presenting abilities of monocytes and dendritic cells, which may contribute to the presentation of self-antigens and the break of immunological self-tolerance [9]. A number of genetic factors have been shown to increase the activity of the type I IFN pathway [10–12], and family studies support the idea that increased type I IFN is a heritable risk factor for SLE [13]. In fact, high levels of type I IFN can be observed in the pre-disease state, and there is a precipitous rise in type I IFN levels 1–2 years prior to disease onset [14, 15].

Circulating functional type I IFN levels are elevated in approximately 50% of patients with SLE, and these levels correlate with SLE-associated autoantibodies, forming a major molecular subset within SLE [16]. Several studies have shown a correlation between the overexpression of IFN-induced genes in circulating blood cells and disease activity in SLE [17–19]. This has been called the "IFN signature", indicating elevated expression of genes that are expected to be upregulated by type I IFN. Because type I IFN has been difficult to measure by traditional methods like ELISA, this signature has been employed in clinical trials as a readout of type I IFN. Approximately 70–80% of patients will have a positive type I IFN signature. This is higher than the percentage of patients with elevated functional type I IFN (50%), and already suggests an issue with this metric. From the earliest studies of the IFN signature, it was noted that type II IFN could not be cleanly separated from type I IFN, as the downstream gene signatures overlap significantly. It is also true that the IFN signature is a collection of genes with anti-viral functions, and these genes can be induced following stimulation of other pathways, including the endosomal Toll-like receptors and cytosolic pattern recognition receptors. Interferon signature studies have also shown that different immune cell types from the same blood sample express different interferon stimulated genes, suggesting that the cellular composition in peripheral blood (percentage of B cells, monocytes, etc.) could potentially influence a whole blood signature. Despite these challenges, Reduction in this IFN signature has been used as a proof-of-concept metric and an outcome measure in many of the clinical trials we will present [20].

A literature search was conducted using electronic search engines (ie, Google Scholar, PubMed) and a combination of different search terms such as “type I Interferon antagonists in development,” and “SLE type I interferon antagonist”. Articles from 2000 and onwards were identified; the final search was conducted on January 25, 2020. During this search approximately 30+ articles discussing therapeutics currently in development were screened. A broad array of therapeutics currently undergoing clinical development that target distinct aspects of SLE’s complex pathogenesis were identified. Some examples of therapeutic targets undergoing clinical development include inflammatory cytokines, interferons, intracellular signaling pathways, B cells and plasmacytoid dendritic cells [21]. To narrow down the scope of the review, the inclusion criteria was changed to identify therapeutics that target the type I IFN pathway, specifically IFNAR Subunit 1 and IFN-α. Therapeutics that modulate downstream effects of IFN-α were excluded, such as JAK inhibitors. While JAK inhibitors may impact type I IFN signaling, they also impact multiple other cytokine signals and this drug category seemed too different from the other drugs presented to be included in the present review.

In this review, we will discuss emerging therapeutics that have been or are currently in clinical trial development for SLE that directly target the type I IFN pathway. Various type I IFN targeting therapeutic approaches have entered human trials, including administration of anti-cytokine antibodies, blocking the effects of type I IFNs by blocking the type I IFN receptor (IFNAR), and vaccination against IFN-α to induce endogenous anti-IFN antibodies [22].

2. Kinoid Interferon-Kinoid

IFN-α kinoid is an immunotherapeutic vaccine is composed of inactivated human IFN alpha-2B coupled to a keyhole limpet hemocyanin (KLH), a T-helper carrier protein [23, 24]. IFN-kinoid immunization disrupts B-cell tolerance and generates high titers of polyclonal IFN neutralizing antibodies without affecting T-cell tolerance [24],

2.1 Preclinical studies

The administration of this compound was observed to promote the production of IFN-α antibodies. In early animal studies, when IFN-kinoid was administered to human IFN-α transgenic mice it would induce a polyclonal antibody response that neutralized 13 human IFN-α subtypes including IFN-a2b [23]. By neutralizing the IFN alpha subtypes it was observed that the mouse IFN-kinoid vaccine prevented and delayed manifestations of disease flare in lupus-prone mice [23].

2.2 Clinical Studies with IFN-α kinoid

2.2.1 Phase I/II Studies—A phase I/IIa multicenter, staggered dose-escalation study (ClinicalTrials.gov record: NCT01058343) in patients with active SLE showed that IFN-kinoid was well tolerated and worked to induce anti-IFN-α antibodies and down regulate IFN induced gene expression in SLE patients [25]. Patients with a high IFN gene signature who received IFN-kinoid at baseline had significantly decreased IFN-induced gene expression to levels found in healthy individuals. Patients who had high anti-IFN-α titers

experienced a significant increase in serum C3 concentrations in comparison to subjects who had low titers [25].

Results from the study demonstrate the ability of the drug to induce anti-IFN-α antibodies and suggest potential efficacy in SLE [25].

Houssiau et al conducted a 36-week phase IIb, multi-national, randomized, double blind, placebo-controlled study in 185 patients with active, moderate-to-severe, SLE to assess the efficacy and safety of IFN-kinoid (ClinicalTrials.gov record: NCT02665364) [26]. Patients were randomized into the IFN-kinoid or placebo group, receiving 5 intramuscular injections of IFN-kinoid or 0.9% NaCl, respectively. The trial employed two primary measures: 1) the neutralization of IFN gene signature, and 2) clinical response measured by BICLA with corticosteroid tapering. Secondary outcomes measured include the following: SRI-4, SRI-4 with corticosteroids tapering, SELENA-SLEDAI, LLDAS, SLEDAI-K, CLASI, BILAG 2004 Index, and health-related quality of life as assessed by SF36 [26].

By week 36, 98% of patients randomized into the IFN-kinoid group had developed anti-IFN-α binding antibodies. Neutralizing effects occurred in 71% of IFN-kinoid patients prior to week 12 [26].

IFN-kinoid patients experienced a polyclonal response that neutralized multiple interferon-alpha subtypes, and as expected IFN-beta neutralization was not observed [26]. Treatment with IFN-kinoid resulted in a 31% mean reduction of IFN gene signature from baseline to Week 36 in comparison to the placebo group, achieving the biological co-primary endpoint. However, the clinical co-primary endpoint was not met since the modified BICLA response was not statistically significant, although IFN-kinoid was favored by 6.7% as compared to placebo treatment [26].

Despite failing to meet one of the two primary endpoints, secondary endpoints favored the IFN- kinoid group. At week 36, 52% of IFN-kinoid group patients achieved lupus low disease activity state whereas 29.8% of placebo treated patients met this criterion [26]. Approximately 24% of individuals in the IFN-kinoid group experienced a 24% prednisone dose reduction from baseline, resulting in a lower average daily prednisone dose in the IFN-kinoid group as compared to the placebo group [26]. This outcome measure is clinically relevant since corticosteroids have many side effects, and SLE damage accrual has been linked to corticosteroid use [27].

2.2.2 Phase III Studies—

On July 3, 2018, it was announced that IFN-kinoid would be further assessed in a phase III clinical trial [28]. Up to now no phase III IFN-kinoid studies have been initiated.

2.1 Safety and Tolerability

Overall, IFN-kinoid had an acceptable safety profile during the phase IIb trial. IFN-Kinoid patients experienced adverse events with 16% more frequency; as compared to the placebo group (IFN- kinoid patients 40.7%, placebo 24.7%) [26]. Common treatment related adverse events observed in the IFN-kinoid group include: upper respiratory infection (17.6%),

urinary tract infection (12.1%), nasopharyngitis (7.7%), pharyngitis (6.6%), bronchitis (5.5%), injection site induration (5.5%), arthralgia (7.7%), pain in extremity (6.6%) and headache (11.0%). Upper respiratory tract infections and arthralgia were three times more common in the IFN-K group and injection site induration was only observed in this cohort. Headaches were five times more common in IFN-kinoid patients (11.0% in IFN- kinoid vs 2.2% in placebo) [26]. Urinary tract infection rates were relatively similar in both cohorts (12.1% IFN-kinoid and 9.7% in placebo). Although these data are promising, further studies need to be conducted to evaluate patient outcomes and treatment response over time to observe the rate at which a patient might relapse once anti-IFN-α antibodies diminish. The duration of anti-IFN antibodies ranged from 6 months up to 36 months from the subject's last IFN-kinoid injection [23]. This presents an issue with this therapeutic strategy, as once the therapeutic is used it cannot be "turned off" until the antibody response wanes. This could be a problem in the setting of an infection arising during IFN- kinoid treatment.

2.2 Conclusion

Results from phase II trials of IFN-Kinoid corroborate the results observed in previous preclinical and Phase I clinical trials. IFN-Kinoid was well tolerated and has shown some evidence of efficacy in these studies. Approximately 98% of the subjects developed IFN-α binding antibodies. After 36 weeks of use, IFN-kinoid lead to a 31% mean reduction in IFN signature. IFN-kinoid failed to meet one of its clinical endpoints, as there was not a significant change observed in the BICLA response. Further studies to assess the duration of anti-IFN antibodies and the factors that may contribute to a decline in anti-IFN-α antibodies need to be done. Overall, IFN-kinoid could be a promising therapeutic for moderate to severe SLE, and phase III studies will be important to assess both efficacy and durability of response.

3. Anti-IFN-α Antibodies

3.1 Rontalizumab

Rontalizumab, formerly known as 9f3v13, is a humanized IgG1 monoclonal antibody designed to bind and neutralize human IFN-α subtypes [29, 30]. Rontalizumab binds to a site on IFN-αs that blocks their interaction with the type I IFN receptor (IFNAR) [30].

3.1.1 Pharmacodynamics, pharmacokinetics and metabolism—

Pharmacokinetic (PK) analysis showed that rontalizumab administration caused a dose-dependent decline in IFN gene signature [29]. The decline of the IFN signature was sustained for about 28 days after the initial dose, and during the 10-week wash out period the IFN signature reverted to baseline levels [29]. Although there was a decline in IFN signature, no subject with a high mean IFN signature was noted to normalize to the level of healthy individuals or to that of patients with a low interferon signature [29].

3.1.2 Clinical Studies with rontalizumab

3.1.2.1 Phase I Studies: A phase I, multi-dose, multi-center study was conducted to evaluate the safety and tolerability of rontalizumab, with a secondary objective of characterizing the pharmacokinetic effects in patients with stable moderately active SLE.

Sixty patients enrolled at 20 centers throughout the United States. Patients were permitted to continue taking concomitant medications, including non-steroidal anti- inflammatory drugs, antimalarials, and corticosteroids at a dose equal or less than 20 mg/day [29].

Mean disease activity at baseline was 3.4± 2.7 on the SELENA-SLEDAI [29]. The IFN signature was measured in patients at baseline and was monitored throughout the duration of the study.

Subjects received either a single, or multiple doses of rontalizumab, administered IV or subcutaneously (SC). Thirteen subjects reported experiencing AEs grade 3 or higher (1 placebo patient, 12 rontalizumab patients). Rontalizumab dosage did not impact the level of AE nor did any of the AEs lead to discontinuation of the study drug [29]. The most commonly reported adverse events were upper respiratory tract infections, headaches, nausea, vomiting, and urinary tract infections. Infections such as urinary tract infections, herpes reactivation, and unspecified viral infections occurred at a higher rate in the rontalizumab group than in the placebo group, 81.3% vs. 75%, respectively. There was only one reported case of malignancy [29]. Overall, rontalizumab demonstrated an acceptable safety profile which was similar to other drugs used to treat SLE.

3.1.2.2 Phase II Studies: ROSE (Rontalizumab in SLE), was a phase II, multicenter study undertaken to evaluate the safety and efficacy of Rontalizumab in moderate to severe SLE patients. The study comprised of two, 24-week, placebo-controlled, sub studies that had the following primary end goal: achieving reduction of all BILAG A domains present at randomization to BILAG B; or reducing from BILAG B to BILAG C; or no new BILAG A or more than one new BILAG B [31]. Secondary outcome measures were included to observe the proportion of patients who achieved the SLE response index (SRI)-4 response at week 24. Exploratory aims were set to study the percent of patients whom decreased use of steroids and flare rates as defined by the SELENA-SLEDAI, as well as the treatment response by patients stratified by baseline IFN signature metric [31].

238 subjects enrolled and were randomized to receive either Rontalizumab or placebo IV monthly for a total of 20 weeks. In part II of the study, randomized subjects either received SC doses of Rontalizumab or placebo every 2 weeks for 22 weeks. IFN signature high vs. low patients did not differ in baseline disease activity, however IFN signature high subjects were more likely to have anti-dsDNA autoantibodies in comparison to IFN signature low patients [31]. Surprisingly, IFN signature low patients were more responsive to rontalizumab as compared to IFN signature high patients. Analysis of disease flares showed that there was a reduction in flares predominantly in IFN signature low patients [31].

These results are paradoxical, as it would be expected that the drug would work better in those who have the targeted pathway activated to the greatest degree. Given the partial neutralization of the IFN signature noted above, it is possible that the drug was not able to fully reduce pathogenic type I IFN signaling in SLE patients with a high signature. Ultimately, Rontalizumab did not meet its primary efficacy endpoint, and development was discontinued.

3.1.3 Conclusions—Although Rontalizumab had an acceptable safety profile, it failed to meet its primary efficacy endpoint, as subjects did not display a reduction in BILAG scores after 24 weeks. It was hypothesized that individuals with a high IFN signature would most benefit from a therapeutic that aimed to block IFN-α [29]. Surprisingly, the therapeutic appeared to benefit subjects with a low IFN signature rather than individuals with a high IFN signature. It is possible that this agent did not provide sufficient type I IFN blockade to reduce the signature and the biological effect of type I IFN in the high IFN patients, and this could be why the beneficial effect was only observed in the low IFN subjects.

3.2 Sifalimumab

Sifalimumab, formerly MEDI-545, is a human IgG1K monoclonal antibody that binds to IFN-α preventing IFN-α signaling through its receptor, IFNAR [32].

3.2.1 Pharmacodynamics, Pharmacokinetics and Metabolism—PK and PD exploratory analysis was completed as part of the phase I study, demonstrating that the PK of sifalimumab was linear and dose proportionate. After multiple doses, serum sifalimumab accumulated 2–3 fold and reached a steady state by day 84. Mean steady state clearance was low ranging from 0.19 to 0.24 liters per day, with a terminal half-life of 19.9 to 29.1 days across the different sifalimumab cohorts [33].

Post completion of the phase I study, a population PK analysis study compared the impact of a fixed vs body weight adjusted dosing of sifalimumab in a simulated population using a PK model to predict concentration-time profiles following 200, 600, and 1,200 mg monthly dosing [34]. Subject variability such as IFN gene signature, baseline weight, genes, steroid use and dose were observed: <7% of PK differences were explained by this variability, not significant to demonstrate that dosing adjustments would be needed. Based on this analysis fixed dosages were established at 200, 600, and 1,200 mg to be administered monthly [22]. Another population PK analysis was completed post phase IIb, which also supported a fixed dose strategy for sifalimumab [35].

3.2.2 Clinical Studies with sifalimumab

3.2.2.1 Phase I: MI-CP126 (ClinicalTrials.gov record: NCT00299819) was a multicenter, randomized, double blind, placebo controlled, dose-escalation phase Ia study that assessed the safety profile and tolerability of sifalimumab in SLE patients. 69 subjects were randomized to receive one intravenous dose of sifalimumab (0.3, 1, 3, 10 or 30 mg/kg) or placebo [32]. A total of 202 AEs was reported in 33 sifalimumab subjects and 126 AEs in 17 placebo subjects. SLE flare was the most common AE observed that occurred with a higher frequency in placebo subjects [32]. There was no significant difference in the rate of infection between the placebo and the sifalimumab group; 41% and 39% respectively [32]. 2 infections were considered treatment related in the sifalimumab group: sinusitis and an upper respiratory infection [32].

A phase IB study (MI-CP152; ClinicalTrials.gov record: NCT00482989) was conducted to evaluate the safety and tolerability of multiple IV doses of sifalimumab in adults with severe to moderate SLE [33]. This multi-center, double blind, placebo-controlled, 26-week

sequential dose-escalation treatment study consisted of five cohorts (sifalimumab: 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, and 10 mg/kg and placebo) [33]. 161 subjects were randomized to receive sifalimumab and 40 subjects received placebo IV infusions. Patients were categorized according to their type I IFN signature in order to ensure that each treatment cohort was equally balanced according to IFN signature [33].

4.1% of the patients on sifalimumab reported having an SLE flare in comparison to 5% of patients on placebo [33]. The most frequent AEs were urinary tract infections (9.1% in sifalimumab group and 10% in placebo), nausea (5% in sifalimumab and 5% in placebo) and headaches (5% in sifalimumab and 2.5% in placebo) [33]. 82 patients on sifalimumab had mild to moderate infections in comparison to 25 patients on placebo. A total of 3 patients developed malignancies, 2 in the placebo groups and 1 in the sifalimumab group [33].

Disease activity did not differ between the treatment and placebo groups at the completion of the study as measured by the mean change from baseline SELENA-SLEDAI score, however this was a Phase I trial [33]. Petri et al conducted a post hoc analysis to adjust for the use of excess corticosteroids and noted that patients in the sifalimumab group showed a greater mean change in SELENA-SLEDAI score [33].

3.2.2.2 Phase II: A phase IIb trial was conducted (ClinicalTrials.gov record: NCT01283139) to assess the efficacy and safety of Sifalimumab in adults with moderate to severe SLE who had inadequate response to standard of care treatment for SLE. Primary outcome measures included reducing Systemic Lupus Erythematosus Responder Index (SRI) 4. Secondary outcome measures included patients with a greater than or equal to 10 mg/day oral prednisone dose at baseline being able to reduce to 7.5 mg/day or less.

432 patients were enrolled and randomized into 4 treatment cohorts (108 Placebo, 108 Sifalimumab 200 mg, 109 sifalimumab 600 mg, 107 sifalimumab 1200 mg) which were administered monthly [36]. Results from this 52-week randomized, double-blind, placebo-controlled study demonstrated that patients receiving sifalimumab achieved the primary end point with improvements peaking at week 24 and then leveling off [36]. A higher percentage of patients on sifalimumab showed improvement in skin, mucocutaneous, and musculoskeletal manifestations of lupus. More sifalimumab patients met the criteria for tapering prednisone to ≤7.5 mg/day as compared to placebo. Post hoc analysis of the data separating patients according to interferon signature showed that substantial improvements were seen in SRI 4 and BICLA in high IFN patients as compared to placebo, however only 19% of the overall study population was low IFN so comparison is limited.

The most common adverse events were worsening of SLE manifestations, urinary tract infections, headaches, and upper respiratory tract infections. These adverse events occurred in both sifalimumab and placebo groups with similar frequencies with the exception of herpes zoster infections, which was observed with higher frequency in the sifalimumab group. Five deaths were documented during the double-blind portion; none of the deaths were attributed to Sifalimumab. Two grade 4 life- threatening infections were reported in Sifalimumab patients: bacterial colitis and bacterial meningitis [36].

Another Sifalimumab Phase II, open-label study (ClinicalTrials.gov record: NCT01031836) consisted of a 52-week initial and long-term extension in Japanese patients. Thirty patients enrolled in Stage I and 21 patients enrolled in Stage II and received ascending doses of Sifalimumab intravenous and subcutaneous. Outcomes of this study showed that this drug was well tolerated, and comparably safe as shown in the phase Ib (MI-CP152) study [37]. Despite some positive findings as noted above, this drug was not taken forward to phase III studies.

3.2.3 Conclusions—Overall, Sifalimumab was observed to have an acceptable safety and tolerability profile. Despite some positive findings in phase II studies, including that that individuals with a high IFN gene signature had substantial improvements in a post-hoc analysis, this drug was not taken forward. If this therapeutic had been advanced to phase III studies, it would have been very interesting to see the results in the high IFN group of patients, and whether this subgroup might have benefited from the therapeutic.

3.3 JNJ-55920839

JNJ-55920839 is a monoclonal antibody which binds both IFN-α and IFN-ω [21, 38].

3.3.1 Phase I—A phase I, randomized, double-blind single ascending dose study of JNJ-55920839 in healthy subjects and multi-dose study of this therapeutic in mild to moderate SLE was completed on September 2018. According to information on clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT02609789), 72 participants have been enrolled to date, all subjects received a single dose of JNJ-55920839 and SLE patients received additional doses on day 15, 29, 43, 57 and 71 days since initial administration [39].

3.3.2 Conclusion—There is limited information available on JNJ-55920839. Presently, no results have been posted for this study.

3.4 AGS-009

AGS-009 is a humanized immunoglobulin G4, monoclonal anti-IFN-α antibody that binds and neutralizes IFN-α [40].

3.4.1 Pharmacodynamics, Pharmacokinetics and metabolism—Pharmacodynamics demonstrated that the peak serum concentration of AGS-009 increased in proportion to the dose administered. Half-life for this therapeutic was observed to be constant at 11–20 days across the dose groups.

3.4.2 Phase I—A phase Ia multicenter, randomized, double blind, placebo-controlled single dose escalation study was conducted in adults with mild to moderate SLE (ClinicalTrials.gov Record: NCT00960362). Twenty-five subjects were randomized into 6 cohorts at a 3:1 ratio, each receiving a single IV infusion of AGS-009 at 0.01, 0.1, 0.6, 3, 10 and 30 mg/kg or placebo in addition to standard of care treatment. All subjects were monitored and had blood samples drawn before and after 85 days to observe changes in expression levels of 27 IFN-α-inducible genes (IFN signature) and to observe pharmacokinetic (PK) changes [24, 41]. After 12 weeks, AGS-009 was safe and well

tolerated at each dose level with no drug-related SAEs or dose-limiting toxicities [40, 42]. Out of the 21 subjects with SLE, 17 had a high IFN signature. At AGS-009 dose levels above 0.6 mg/kg there was a marked decrease in IFN signature in the SLE patients that was not seen in placebo subjects. AGS-009 has not entered further development stages [43].

3.4.3 Conclusion—AGS-009's phase Ia showed promising results in the 25 subjects that participated in the study. No further studies have been reported using this therapeutic since the release of the phase I clinical trial results at the 2012 EULAR conference.

4. IFNAR Receptor Blocker Anifrolumab

Formerly known as MEDI546, anifrolumab is a human monoclonal antibody that binds to and blocks signaling through the IFNAR receptor, blocking all type I interferon signaling [44]. Anifrolumab has been studied in Phase I, II, and III studies in SLE studies [45].

4.1 Pharmacodynamics, pharmacokinetics and metabolism

Peng et.al conducted a study to understand the mechanism of action of anifrolumab [46]. Anifrolumab crystal structure and docking analysis confirmed that Anifrolumab sterically inhibits type I IFN by binding to IFNAR, and it does not fix complement [44]. IFNAR1 blocking prevents the type I IFN signaling and the auto-amplification loop in which type I IFN signaling can prime stronger subsequent responses to type I IFN. Blocking IFNAR also reduced expression of the costimulatory and cellular activation markers CD80 and CD83 expression of dendritic cells by 30 −50% [45]. Tanaka et al observed that IV anifrolumab serum concentrations reached a steady state by day 85 for those in the 300 mg and 1000 mg cohort in comparison to those in the 100 mg cohort whom reached steady state by day 377 [47]. This was thought to be due to the antigen sink effect which was observed in lower anifrolumab concentrations.

4.2 Clinical studies with anifrolumab

4.2.1 Phase I—A phase I study assessed the safety and tolerability of intravenous and subcutaneous anifrolumab in 30 healthy volunteers. Anifrolumab was observed to be a PK dose-proportional drug that has a peak serum concentration that occurs 4–7 days after injection, concentrations decreased by day 84 of the dose [48].

No concerning safety issues were observed in the phase I trial.

4.2.2 Phase II—MUSE, a phase IIB (ClinicalTrials.gov: NCT01438489), multinational, double blind, randomized study was conducted to evaluate the safety and tolerability of anifrolumab in adults with moderate-to-severe lupus, excluding neuropsychiatric SLE and lupus nephritis [49]. 305 randomized participants received one of the following: 300 mg of anifrolumab IV infusion, 1000 mg anifrolumab IV infusion, or placebo infusion every 4 weeks for 48 weeks in addition to their standard of care therapy. The primary endpoint was the percent of subjects whom achieved SRI 4 response at week 24th with a reduction in corticosteroid use of ≤10 mg/day [49]. Secondary endpoints included SRI response rates at week 52 with a sustained oral corticosteroid reduction from week 40 to week 52 [49].

The primary efficacy point was significant after an adjustment analysis was done to show that there was a greater SRI-4 response in the anifrolumab group in comparison to placebo. This was more pronounced in the high IFN subpopulation, but notably the high IFN group was 75% of the subjects enrolled [49]. Interestingly, the response rate did not seem to differ between the high and low IFN groups, but instead the placebo response rate was higher in the low IFN group as compared to the high IFN group. Serious adverse event rates were similar across all groups (18.8% of subjects in the placebo group, 16.2% in the anifrolumab 300 mg group and 17.1% in the anifrolumab 1000 mg group) [49].

Herpes zoster Infections were observed in approximately 5.1% and 9.5% of patients in the anifrolumab 300 mg and 1000 mg groups respectively in comparison to 2% in the placebo group. The rate of influenza was observed to be greater in the anifrolumab 300 mg (6.15%) and anifrolumab 1000-mg group (7.6%) than in the placebo group (2%) [49].

Post-hoc analysis of the MUSE data demonstrated that anifrolumab treatment led to improvement in arthritis and rash. Clinical outcomes showed that 44.3 % of patients treated with anifrolumab showed resolution of rash as compared to 14.8% on placebo [50]. Merrill et al compared high IFN subjects to low IFN subjects, and 49.3% of those in the IFN-high group treated with anifrolumab experienced a resolution in rash in comparison to 10.8% in the placebo cohort [50]. When analyzing IFN-low patients, no difference was noted in the percent of rash resolution between patients on anifrolumab and placebo (28.6% and 26.1%, respectively) [50]. Another intravenous (IV) anifrolumab phase 2 study was conducted to evaluate the safety and efficacy of anifrolumab (formerly known as MEDI-546) in Japanese patients with moderate to severe SLE (ClinicalTrials.gov record: NCT01559090). This open-label, phase 2, dose-escalation study consisted of initial treatment and follow up for 48 weeks and followed by long term follow up for 156 weeks [47]. The IFN gene signature was neutralized between days 29 to 422 in the 1000 mg cohort and reached max neutralization at day 393 to 422. In the 300 mg cohort, gene signature neutralization occurred from days 85 to 365 and a max neutralization took place between day 253 and 337[47].

A 52-week phase II study looking at subcutaneous administration of anifrolumab in addition to standard of care treatment was conducted to evaluate PK, PD, safety and tolerability in subjects with a high IFN signature and active skin disease (ClinicalTrials.gov record: NCT02962960) [51, 52]. A total of 36 patients were enrolled: 14 received anifrolumab 150 mg, 13 received anifrolumab 300 mg and 9 received placebo. At week 12 there was more than 75% neutralization of the IFN signature observed in 66.7% of anifrolumab 150 mg subjects, 76.9% in anifrolumab 300 mg, and 11.1% of patients in the placebo group. CLASI score values decreased from baseline predominantly in the 150 mg and 300 mg anifrolumab cohorts in comparison to placebo; −10.2, −13.2 vs −6.3, respectively. Only ten SAEs were reported by 6 patients in the 2 anifrolumab groups. Overall, SC administration of Anifrolumab showed suppression of IFN signature over 52 weeks and was noted to have a nonlinear PK which was dose proportional. The PK/PD values observed to be consistent with studies done using IV anifrolumab and was seen to have a similar safety profile as the other larger IV administration studies in SLE.

4.2.3 Phase III—Anifrolumab was the first type I IFN blocking drug to be tested in phase III trials. TULIP 1 was a multi-national study of anifrolumab for the treatment of SLE consisting of 123 sites in 18 different countries (ClinicalTrials.gov: NCT02446912) [53]. The primary outcome was the percentage of patients achieving an SRI-4 response at week 52 in the anifrolumab 300 mg group vs. placebo in 457 randomized patients. While the primary endpoint was not met in this study, a number of other metrics showed positive results. Patients receiving anifrolumab had a greater decrease in corticosteroid dose from week 40 to week 52 in comparison to placebo [53]. BICLA response was achieved by more patients on anifrolumab 300 mg at week 52 than placebo patients. Likewise changes in SLEDAI-2k and BILAG scores from baseline to week 52 were observed to be greater in the anifrolumab 300 mg group. Other findings demonstrated that those that received the 300 mg anifrolumab IV dose experienced a suppression of the IFN gene signature during an earlier point in their treatment [53]. The frequency of serious adverse events was similar across the treatment groups (16.2% in anifrolumab 300-mg, 17.1% in anifrolumab 1000-mg and 18.8% in placebo) [53].

A second phase III study was run concurrently with TULIP 1, the TULIP 2 trial (ClinicalTrials.gov record: NCT02446899). Similar to the TULIP 1 trial, patients were randomized in a 1:1 ratio to receive intravenous infusions of placebo or 300 mg of anifrolumab every 4 weeks for 48 weeks [54]. The main difference between TULIP 1 and TULIP 2 was that the BICLA was used as the primary end point [54]. A total of 365 patients were randomly assigned (184 anifrolumab group and 184 in the placebo group). 85% of patients in the anifrolumab group completed the intervention and 71.4% completed treatment in the placebo group [54]. BICLA response at week 52 was observed to be 16.3% higher in the anifrolumab group (47.8% in the anifrolumab response and 31.5% in the placebo group). Subpopulation analysis for key secondary end points showed that 48% of patients in the anifrolumab with a high interferon gene signature achieved a BICLA response at week 52. In the subpopulation with low interferon signature 46.7% achieved a BICLA response, this subpopulation counted for 16.9% of total 362 patients whom received treatment. The SRI endpoint was also met in this study, unlike TULIP 1.

Consistent with the MUSE and TULIP 1 study, the BICLA response, CLASI, glucocorticoid reduction, and flare reduction endpoints favored anifrolumab [54]. It is still not clear why one phase III trial met endpoints while the other phase III did not. The TULIP 2 study was smaller but met the SRI-4 endpoint that was missed in TULIP 1. It is likely that these differences reflect the general difficulties of conducting trials in SLE, which we will discuss below.

4.4 Conclusions

The results from Phase I and Phase II trials demonstrated the efficacy, safety, and tolerability of anifrolumab in those with moderate-to-severe SLE. Anifrolumab neutralized the IFN gene signature and conferred a reduction in oral corticosteroid use and rash in the high IFN gene signature group. These results demonstrate the potential of anifrolumab as a therapeutic agent; it could be a first-in-class type I IFN antagonist for use in moderate-to-severe SLE. Based on the positive results from the TULIP II phase III trial and the positive results across

most metrics used in the studies presented, it appears that Anifrolumab will most likely be filed for FDA approval [51].

5 Conclusions

Despite some difficulties, it seems likely that a therapeutic targeting type I IFN in SLE will progress to clinical utility. Each of the studies presented above documented some evidence of positive response, and an acceptable side-effect profile, and in aggregate the data from these individual trials seems more convincing than any one individual trial. Given the unmet clinical need in SLE, a new type I IFN blocking drug would be a welcome addition to the clinician's toolbox. It seems that the difficulties and inconsistencies observed in the type I IFN drug development process are likely to be shared with other SLE drugs in the future and calls for serious consideration of adjusting standards for approval and continued efforts to improve trial design and measures of disease activity. In general, these studies support subgroup effects in SLE, with the drugs resulting in different outcomes in the high and low IFN groups. It seems likely that these groups and the way we indicate them using the IFN signature may not be specific enough, and this issue is discussed in more detail below in the Expert Opinion section.

Hopefully with continued research and drug development in SLE, we will improve our understanding of disease pathogenesis and achieve more effective and efficient drug therapy.

6 Expert Opinion

Six therapeutics have been designed to inhibit type I IFN for the treatment of SLE. Of these six therapeutics, Anifrolumab has taken forward to phase III, and it seems likely that IFN-Kinoid will advance to this stage as well. Anifrolumab will likely be filed for FDA approval after meeting the primary endpoint in one of the two phase III trials that were conducted. On the other hand, rontalizumab failed to meet phase II primary endpoints and was discontinued, and sifalimumab development was also discontinued [55]. Data for each of these drugs is summarized in Table 1, and extensive details regarding each of the trials is provided in Table 2. One thought about why anifrolumab has advanced while other agents have not is that anifrolumab blocks IFNAR, which would interrupt signals from both IFN-β and IFN-α, while the other strategies block only IFN-α. Thus far there is more evidence for the role of IFN-α than IFN-β in SLE pathogenesis. In blood studies, the majority of circulating functional type I IFN is IFN-α [13]. IFN-β could still be active at the level of the tissue, such as the bone marrow [56] and sites of inflammation, but this of course is more difficult to assess. A theoretical concern is that there could be more infectious side-effects from complete blockade of the type I IFN receptor as compared to strategies that block IFN-α but preserve IFN-β. Thus far, the anifrolumab strategy of blocking both IFN-α and IFN-β together has demonstrated the most efficacy, and the side effects reported do not seem to be any more than those observed with agents that block IFN-α alone._ There are some other type I IFNs such as IFN-ω which again have less evidence for their importance in SLE pathogenesis, but it is possible that some of the improved efficacy from anifrolumab could be the result of blocking these IFNs as well.

While there is strong evidence that the type I IFN pathway plays a pathogenic role in SLE, the results from these trials are still not impressive overall, and other examples from rheumatic disease such as anti-TNF-α therapy in rheumatoid arthritis were much more uniformly and consistently positive. One of the features of SLE that might be confounding our efforts is that often many immune system pathways are turned on concurrently. We find that in the high type I IFN patients, there are also high levels of BAFF [57]. We have also shown that type II IFN levels are correlated with type I IFN, and patients with nephritis commonly have elevations in both of these IFNs simultaneously [58]. TNF-α levels are elevated in many SLE patients, and this cytokine seemed to assort independently from type I IFN, with a slight positive correlation [59]. When looking at stimulated cytokine responses in immune cells from SLE patients, there are many differences between those patients with high and low type I IFN, supporting the idea that type I IFN marks major biological groups within SLE [60]. These data suggest that it may not be enough to target only one cytokine or pathway at a time in SLE patients with active disease. Multi-cytokine strategies would be of interest in SLE, and while there could be more risk of side effects, we continue to be plagued by lack of efficacy in our single cytokine targeting trials thus far. Each of the additional cytokines mentioned above could potentially be targeted in a multiple cytokine strategy, as there are anti-BAFF and anti-TNF agents currently available, and an anti-type II IFN agent AMG-811 is currently being developed.

While the whole blood IFN signature has been useful as an easy metric in clinical trials, it may not be the most helpful metric as a biological readout for anti-type I IFN drugs. As noted in the introduction, the contribution of type II IFN to the signature and the various contributions from different immune cells in different proportions between patients cannot be well controlled. Also, the fact that the signature is present in 70–80% of patients [19], while an elevation of functional type I IFN is only present in 50% [16] supports the idea that the signature only partially reflects type I IFN receptor signaling. Different studies have frequently chosen different genes to include to compose their own “signature”, but these are largely interchangeable, and when data from different companies have been compared using alternate signatures, the results have not changed significantly. This is due to the fact that the genes in the IFN signature tend to be very highly correlated with each other [61], and many different combinations could be chosen that would produce the same result. Using a functional assessment of type I IFN in blood as in [16] to determine those patients in whom type I IFN inhibitors should be used might be a more effective approach than using IFN signature. This would result in the exclusion of those patients who have an IFN signature but no elevation of functional type I IFN. This group of patients is interesting, and they could represent a different immunological subgroup that is more dependent upon type II IFN or pattern recognition receptor signaling. The single-molecule array (Simoa) digital ELISA technology [62] is another approach that could be useful for the sensitive detection of IFN-α. This has been used to study cohorts of autoimmune disease patients with success [62], including SLE and other autoimmune conditions with high type I IFN levels. This assay can currently only be used to measure IFN-α2, while functional assays can assess all type I IFNs, but it seems likely that the company will develop an assay for IFN-β soon.

It is likely that some of the difficulties in moving type I IFN blocking drugs along the clinical pipeline relates to difficulties in designing and conducting SLE trials more generally.

As noted in the introduction, many lines of evidence implicate type I IFN in SLE pathogenesis, and the drugs discussed in this review all demonstrated an ability to inhibit this pathway. Difficulties in SLE clinical trials include significant background therapy such as corticosteroids and other immunosuppressants which can mask experimental drug effects. Also, the composite outcome measures used in SLE trials are not ideal. SLE can affect multiple body systems, and the currently used outcome measures integrate findings across multiple body systems but can obscure findings in individual systems.

While the anifrolumab TULIP I study failed to meet its primary endpoint, it met many secondary endpoints, and the TULIP 2 trial which was very similar and slightly smaller met the endpoint that was not met in TULIP 1. The majority of clinical endpoints were met in the anifrolumab phase II and in each of the phase III studies, and the bulk of the evidence supports a beneficial effect of anifrolumab in SLE, but the endpoint chosen as primary in TULIP 1 was not met. This example suggests that reliance on a single outcome measure as a primary endpoint may lead to unnecessary failures in SLE studies, and that the ability to consider multiple outcomes could allow more drugs to progress toward the clinic [63].

Improvements in trial design including control of background medications and improved outcome measures could also be helpful, although each of these is difficult given the varied clinical course and manifestations observed in SLE. Furie et al notes that although the SRI-4 and BICLA are comprised of the same components, the endpoints are optimal in different situations. The SRI-4 requires that there be a resolution of the symptoms before the score can change, while the BICLA can show improvement in separate organ domains and could be more sensitive to specific improvements [53]. New drugs are undeniably needed for the treatment of SLE, and given the difficulties in conducting trials in SLE, additional flexibility in endpoints and the definition of success should be considered seriously [63]. Also, as we are able to define molecular subsets in SLE, we may be able to better direct treatments to specific molecular features of disease. This would be a major advance in SLE, and the above clinical trials have taken steps in this direction by doing stratified analyses based upon type I IFN signature. There is clearly more work to do before we are able to achieve the goal of personalized medicine in SLE and other rheumatic diseases [64].

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers

*=of importance, **= of considerable import

1. Tsokos GC, Systemic lupus erythematosus. N Engl J Med, 2011. 365(22): p. 2110–21. [PubMed: 22129255]
2. Sinicato NA, et al., Defining biological subsets in systemic lupus erythematosus: progress toward personalized therapy. Pharmaceut Med, 2017. 31(2): p. 81–88. [PubMed: 28827978]
3. Niewold TB, Interferon alpha as a primary pathogenic factor in human lupus. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research, 2011. 31(12): p. 887–92.
4. Ghodke-Puranik Y. and Niewold TB, Immunogenetics of systemic lupus erythematosus: A comprehensive review. J Autoimmun, 2015. 64: p. 125–36. [PubMed: 26324017]
5. Pestka S, Krause CD, and Walter MR, Interferons, interferon-like cytokines, and their receptors. Immunol Rev, 2004. 202: p. 8–32. [PubMed: 15546383]
6. Chasset F. and Arnaud L, Targeting interferons and their pathways in systemic lupus erythematosus. Autoimmunity Reviews, 2018. 17(1): p. 44–52. [PubMed: 29108825]
7. Shrivastav M. and Niewold TB, Nucleic Acid Sensors and Type I Interferon Production in Systemic Lupus Erythematosus. Frontiers in immunology, 2013. 4: p. 319. [PubMed: 24109483]
8. Lopez de Padilla CM and Niewold TB, The type I interferons: Basic concepts and clinical relevance in immune-mediated inflammatory diseases. Gene, 2016. 576(1 Pt 1): p. 14–21. [PubMed: 26410416]
9. Blanco P, et al., Induction of dendritic cell differentiation by IFN-alpha in systemic lupus erythematosus. Science, 2001. 294(5546): p. 1540–3. [PubMed: 11711679]
10. Kariuki SN, et al., Trait-stratified genome-wide association study identifies novel and diverse genetic associations with serologic and cytokine phenotypes in systemic lupus erythematosus. Arthritis Res Ther, 2010. 12(4): p. R151.
11. Kariuki SN, et al., Genetic analysis of the pathogenic molecular sub-phenotype interferon-alpha identifies multiple novel loci involved in systemic lupus erythematosus. Genes and immunity, 2015. 16(1): p. 15–23. [PubMed: 25338677]
12. Ghodke-Puranik Y, et al., Novel genetic associations with interferon in systemic lupus erythematosus identified by replication and fine-mapping of trait-stratified genome-wide screen. Cytokine, 2019.
13. Niewold TB, et al., High serum IFN-alpha activity is a heritable risk factor for systemic lupus erythematosus. Genes Immun, 2007. 8: p. 492–502. [PubMed: 17581626]
14. Munroe ME, et al., Altered type II interferon precedes autoantibody accrual and elevated type I interferon activity prior to systemic lupus erythematosus classification. Annals of the rheumatic diseases, 2016. 75(11): p. 2014–2021. [PubMed: 27088255] **Study demonstrating the elevation of IFNs in the pre-disease stage of SLE
15. Niewold TB, et al., Serum type I interferon activity is dependent on maternal diagnosis in anti-SSA/Ro-positive mothers of children with neonatal lupus. Arthritis Rheum, 2008. 58(2): p. 541–6. [PubMed: 18240214]
16. Weckerle CE, et al., Network analysis of associations between serum interferon-alpha activity, autoantibodies, and clinical features in systemic lupus erythematosus. Arthritis Rheum, 2011. 63(4): p. 1044–53. [PubMed: 21162028]
17. Kirou KA, et al., Activation of the interferon-alpha pathway identifies a subgroup of systemic lupus erythematosus patients with distinct serologic features and active disease. Arthritis Rheum, 2005. 52(5): p. 1491–503. [PubMed: 15880830]
18. Bennett L, et al., Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. J Exp Med, 2003. 197(6): p. 711–23. [PubMed: 12642603]

19. Baechler EC, et al., Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci U S A, 2003. 100(5): p. 2610–5. [PubMed: 12604793]
20. Wampler Muskardin TL and Niewold TB, Type I interferon in rheumatic diseases. Nature Reviews Rheumatology, 2018. 14(4): p. 214–228. [PubMed: 29559718] **Review of type I IFNs in SLE and other rheumatic diseases
21. Felten R, et al., The 2018 pipeline of targeted therapies under clinical development for Systemic Lupus Erythematosus: a systematic review of trials. Autoimmunity Reviews, 2018. 17(8): p. 781–790. [PubMed: 29885544]
22. Greth W, et al., Targeting the interferon pathway with sifalimumab for the treatment of systemic lupus erythematosus. 2017. 9(1): p. 57–70.
23. Ducreux J, et al., Interferon α kinoid induces neutralizing anti-interferon α antibodies that decrease the expression of interferon-induced and B cell activation associated transcripts: analysis of extended follow-up data from the interferon α kinoid phase I/II study. Rheumatology (Oxford, England), 2016. 55(10): p. 1901–1905.
24. Mathian A, et al., Targeting Interferons in Systemic Lupus Erythematosus: Current and Future Prospects. Drugs, 2015. 75(8): p. 835–846. [PubMed: 25940912]
25. Lauwerys BR, et al., Down-regulation of interferon signature in systemic lupus erythematosus, patients by active immunization with interferon α–kinoid. 2013. 65(2): p. 447–456.
26. Houssiau FA, et al., IFN-alpha kinoid in systemic lupus erythematosus: results from a phase IIb, randomised, placebo-controlled study. Ann Rheum Dis, 2020. 79(3): p. 347–355. [PubMed: 31871140] *Phase II trial of an IFN antagonist in SLE
27. Apostolopoulos D, et al., Factors associated with damage accrual in patients with systemic lupus erythematosus with no clinical or serological disease activity: a multicentre cohort study. The Lancet Rheumatology, 2020. 2(1): p. e24-e30.
28. Neovacs, Neovacs Announce the Results of its Phase IIB study for IFNα KINOID in the treatment, of Lupus which allows to proceed with the clinical development into Phase III. 2018.
29. McBride JM, et al., Safety and pharmacodynamics of rontalizumab in patients with systemic lupus erythematosus: Results of a phase I, placebo-controlled, double-blind, dose-escalation study. 2012. 64(11): p. 3666–3676.
30. Maurer B, et al., Structural basis of the broadly neutralizing anti-interferon-α antibody, rontalizumab. 2015. 24(9): p. 1440–1450.
31. Kalunian KC, et al., A Phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). 2016. 75(1): p. 196–202.*Phase II trial of an IFN antagonist in SLE
32. Merrill JT, et al., Safety profile and clinical activity of sifalimumab, a fully human anti-interferon α monoclonal antibody, in systemic lupus erythematosus: a phase I, multicentre, double-blind randomised study. 2011. 70(11): p. 1905–1913.
33. Petri M, et al., Sifalimumab, a human anti-interferon-alpha monoclonal antibody, in systemic lupus erythematosus: a phase I randomized, controlled, dose-escalation study. Arthritis Rheum, 2013. 65(4): p. 1011–21. [PubMed: 23400715]
34. Narwal R, Roskos LK, and Robbie GJ, Population pharmacokinetics of sifalimumab, an investigational anti-interferon-α monoclonal antibody, in systemic lupus erythematosus. Clinical pharmacokinetics, 2013. 52(11): p. 1017–1027. [PubMed: 23754736]
35. Zheng B, et al., Population pharmacokinetic analysis of sifalimumab from a clinical phase IIb trial in systemic lupus erythematosus patients. 2016. 81(5): p. 918–928.
36. Khamashta M, et al., Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. 2016. 75(11): p. 1909–1916.*Phase II trial of an IFN antagonist in SLE
37. Takeuchi T, et al., Safety and tolerability of sifalimumab, an anti-interferon-α monoclonal antibody, in Japanese patients with systemic lupus erythematosus: A multicenter, phase 2, open-label study. Modern Rheumatology, 2020. 30(1): p. 93–100. [PubMed: 30791804]
38. Crow MK and Rönnblom L, Report of the inaugural Interferon Research Summit: interferon in inflammatory diseases. 2018. 5(1): p. e000276.

39. Chugh PK, Lupus: Novel therapies in clinical development. European Journal of Internal Medicine, 2012. 23(3): p. 212–218. [PubMed: 22385876]
40. Tcherepanova I, et al., SAT0193 Results of a randomized placebo controlled phase ia study of AGS-009, a humanized anti-interferon-α monoclonal antibody in subjects with systemic lupus erythematosus. 2013. 71(Suppl 3): p. 536–537.
41. Therapeutics A, Argos Therapeutics Initiates Dosing of Patients in Phase 1 Clinical Trial of Monoclonal Antibody-Based Therapy for Treatment of Systemic Lupus Erythematosus. 2010.
42. Farinha F. and D.A.J.D.o.t.F. Isenberg, Advances in IFN-alpha targeting-approaches for SLE treatment. 2015. 40(9): p. 129–129.
43. Pan L, et al., Immunological pathogenesis and treatment of systemic lupus erythematosus. World Journal of Pediatrics, 2020. 16(1): p. 19–30. [PubMed: 30796732]
44. Riggs JM, et al., Characterisation of anifrolumab, a fully human anti-interferon receptor antagonist antibody for the treatment of systemic lupus erythematosus. 2018. 5(1): p. e000261.
45. Felten R, et al., Spotlight on anifrolumab and its potential for the treatment of moderate-to- severe systemic lupus erythematosus: evidence to date. Drug design, development and therapy, 2019. 13: p. 1535–1543.
46. Peng L, et al., Molecular basis for antagonistic activity of anifrolumab, an anti-interferon–α receptor 1 antibody. mAbs, 2015. 7(2): p. 428–439. [PubMed: 25606664]
47. Tanaka Y, et al., Safety and tolerability of anifrolumab, a monoclonal antibody targeting type I interferon receptor, in Japanese patients with systemic lupus erythematosus: A multicenter, phase 2, open-label study. Modern Rheumatology, 2020. 30(1): p. 101–108. [PubMed: 30793642]
48. Tummala R, et al., Safety, tolerability and pharmacokinetics of subcutaneous and intravenous anifrolumab in healthy volunteers. 2018. 5(1): p. e000252.
49. Furie R, et al., Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis & rheumatology (Hoboken, N.J.), 2017. 69(2): p. 376–386.
50. Merrill JT, et al., Anifrolumab effects on rash and arthritis: impact of the type I interferon gene signature in the phase IIb MUSE study in patients with systemic lupus erythematosus. Lupus science & medicine, 2018. 5(1): p. e000284-e000284.
51. Bruce I, et al. PK/PD, safety and exploratory efficacy of subcutaneous anifrolumab in SLE: a phase-II study in interferon type I high patients with active skin disease. in ARTHRITIS & RHEUMATOLOGY. 2019. WILEY 111 RIVER ST, HOBOKEN 07030–5774, NJ USA.
52. Anderson E. and Furie R, Anifrolumab in systemic lupus erythematosus: current knowledge and future considerations. 2020. 12(5): p. 275–286.
53. Furie RA, et al., Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. The Lancet Rheumatology, 2019. 1(4): p. e208-e219.**Pivotal phase III study of an IFN antagonist in SLE
54. Morand EF, et al., Trial of Anifrolumab in Active Systemic Lupus Erythematosus. NEJM 2019. 382(3): p. 211–221. [PubMed: 31851795] **Pivotal phase III study of an IFN antagonist in SLE
55. Isenberg DA and Merrill JT, Why, why, why de-lupus (does so badly in clinical trials). Expert Review of Clinical Immunology, 2016. 12(2): p. 95–98. [PubMed: 26786849]
56. Gao L, et al., Bone marrow mesenchymal stem cells from patients with SLE maintain an interferon signature during in vitro culture. Cytokine, 2020. 132: p. 154725.
57. Ritterhouse LL, et al., B lymphocyte stimulator levels in systemic lupus erythematosus: higher circulating levels in African American patients and increased production after influenza vaccination in patients with low baseline levels. Arthritis Rheum, 2011. 63(12): p. 3931–41. [PubMed: 22127709]
58. Oke V, et al., High levels of circulating interferons type I, type II and type III associate with distinct clinical features of active systemic lupus erythematosus. Arthritis Res Ther, 2019. 21(1): p. 107. [PubMed: 31036046]
59. Weckerle CE, et al., Large-scale analysis of tumor necrosis factor alpha levels in systemic lupus erythematosus. Arthritis and rheumatism, 2012. 64(9): p. 2947–52. [PubMed: 22488302]

60. Thanarajasingam U, et al., Type I Interferon Predicts an Alternate Immune System Phenotype in Systemic Lupus Erythematosus. ACR Open Rheumatol, 2019. 1(8): p. 499–506. [PubMed: 31777831]

61. Kirou KA, et al., Coordinate overexpression of interferon-alpha-induced genes in systemic lupus erythematosus. Arthritis Rheum, 2004. 50(12): p. 3958–67. [PubMed: 15593221]

62. Rodero MP, et al., Detection of interferon alpha protein reveals differential levels and cellular sources in disease. J Exp Med, 2017. 214(5): p. 1547–1555. [PubMed: 28420733]

63. Salmon JE and Niewold TB, A Successful Trial for Lupus — How Good Is Good Enough? 2019. 382(3): p. 287–288.

64. Wampler Muskardin TL, et al., Lessons from precision medicine in rheumatology. Mult Scler, 2020: p. 1352458519884249.

Article Highlights:

- Type I IFN is a primary pathogenic factor in SLE that is associated with high disease activity.
- Overexpression of IFN-induced genes in circulating blood cells known as the IFN signature is used as a metric to evaluate therapeutic effectiveness.
- Type I IFN antagonist therapy has shown efficacy and safety, and is a promising strategy in SLE
- Although development of rontalizamub and sifalimumab was discontinued; IFN-kinoid will be further assessed in a phase III clinical trial
- Results from phase III trials of anifrolumab showed that many metrics improved, including IFN gene signature, arthritis, and rash, but only one of the two-phase III trials met its primary endpoint.
- Conducting trials in SLE continues to be difficult due to disease heterogeneity, the need for background therapy, and the use of composite outcome measures.

Type I Interferon Antagonist	IFN Pathway Target	ClinicalTrial.gov Identifier	Study Phase	References
Interferon α-Kinoid	IFN-α	NCT01058343	I/II	[23, 65] [25]
		NCT02665364	IIb	[26]
Rontalizumab	IFN-α	NCT00541749	I	[29]
		NCT00962832	II	[31]
Sifalimumab (MEDI 545)	IFN-α	NCT00299819	Ia	[32]
		NCT00482989	Ib	[34] [33]
		NCT01031836	II	[37]
		NCT00657189	IIa	https://clinicaltrials.gov/ct2/show/record/NCT00657189?term=anti+interferon [24]
		NCT01283139	IIb	[36]
		NCT00979654	II	https://clinicaltrials.gov/ct2/show/NCT00979654
Anifrolumab (MEDI 546)	IFNAR-1	NCT02601625	I	[48]
		NCT01438489	II	[49]
		NCT02962960	II	https://acrabstracts.org/abstract/pk-pd-safety-and-exploratory-efficacy-of-subcutaneous-anifrolumab-in-sle-a-phase-ii-study-in-interferon-type-i-high-patients-with-active-skin-disease/
		NCT01559090	II	[47]
		NCT01753193	II	https://acrabstracts.org/abstract/a-phase-2-open-label-extension-study-to-evaluate-long-term-safety-of-anifrolumab-in-adults-with-systemic-lupus-erythematosus/
		NCT02547922	II	https://www.clinicaltrials.gov/ct2/show/NCT02547922
		NCT02446912	III	[45]
		NCT02446899	III	[54]
		NCT02794285	III	https://clinicaltrials.gov/ct2/show/NCT02794285
JNJ-55920839	IFN-α/ω	NCT02609789	I	[21] [38]
AGS-009	IFN-α	NCT00960362	Ia	[40]

Type I Interferon Antagonist	Mechanism of Action	NCT Identifier	Study Phase	Sample Size	Race and Ethnicity	Primary Outcome	Secondary Outcome	Genes and effect on IFN signature	References
Interferon α-Kinoid	IFN-Kinoid immunization generates high titers of polyclonal neutralizing antibodies against IFN-α	NCT01058343	I/II	Total: 28 patients (100% female) • 21 treated with IFN-K • 7 patients treated with Placebo	• 96% Caucasian (27) • 4% Asian (1)	AEs included infections and SLE flares, and the two SAEs were SLE flares, one in the treatment and one in the placebo group.	6 IFN-K receiving subjects continued to have antibodies that were detectable 6 months after their last follow up visit (range of peak response: 168–1558 days)	The effect of IFN-K was assessed using a 31 probe set in the expression of 21 IFN signature genes as described by Yao et al [65]. Individuals who had a positive IFN signature were observed to experience a decrease in IFN-inducible gene expression in comparison to those receiving placebo treatment.	[23] [25]
		NCT02665364	IIb	Total: 184 patients (93% female) • 91 treated with IFN-K • 93 on placebo	• 1% Black (2) • 14.1% Asian (26) • 70.6% Caucasian/ Hispanic (130) • 14.1% Other (26)	The biological efficacy measure was met as treatment with IFN-K induced a type I IFN gene mean reduction of 31% from baseline to week 36.	Clinical response measured by BICLA with corticosteroid tapering of ≤5 mg or equivalent per day at week 24 and with no increase until week 36. The BICLA response difference was only 6.7% in favor of IFN-K over placebo and so the clinical efficacy measure was not met.	The IFN gene signature was tested on a selection of 10 IFN-inducible genes (FIT3, MX1, ISG15, IFIT1, IFI6, OAS2, HERC5, LY6E, IFI27 and SIGLEC1) known to correlate with IFN signature, which was based on the 21 probe set described in phase I/II trial. Treatment with IFN-K led to a 31% mean reduction in type I interferon gene score at week 36. This was not observed in	[26]

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								placebo treated patients. However, 20/87 patients experienced an increase of IFN gene signature which could be related to a lower immune response against IFN-α.	
			III	**Anticipated**					
Rontalizumab	Rontalizumab is a humanized monoclonal anti-IFN-α antibody that neutralizes 12 IFN-α subtypes	NCT00541749	I	Total: 60 patients (95% female) • 12 patients on placebo • 48 patients treated with Rontalizumab	• 70% Caucasian • 27% African American • 3% Not reported	Both IV and SC administration was generally well tolerated. Most of the reported AE's included urinary tract infections, herpes reactivation, and unspecified viral infections which occurred at a higher rate in the combined Rontalizumab group than placebo group. Despite this higher rate of occurrence, none of the AEs/SAEs were attributed to the therapeutic drug	Overall, PD analysis showed that Rontalizumab was dose proportional whether it was administered as a SC/IV. Rontalizumab administration at dose of 3 mg/kg IV and 10 mg/kg IV induced a substantial decline (>50%) in gene expression when compared to baseline values	The Interferon Signature Mean (ISM) was determined using the average expression level of 7 selected interferon regulated genes at baseline. Interferon regulated gene expression levels decreased following the administration of Rontalizumab in the selected genes (IFI27, MX1, IFI44, IFIT1, OAS1, OAS2, and OAS3) was seen in all patients regardless of ISM designation at baseline.	[29]
		NCT00962832	II	Total: 238 patients (94% female) • 79 placebo	• 46.2% White (110) • 36.5% American Indian or	The primary efficacy point was not met, no significant difference in the percentage of patients who	The secondary efficacy point was the SRI (4) response at week 24. Response rates did not differ in the treatment	IFN-gene expression assessed changes in seven IFN-regulated genes (IFI27, IFI44,	[31]

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				• 159 on Rontalizumab	Alaskan Native (87) • 14.3% Black or African American (34) • 3% Other* (7) • 49.2% Ethnicity: Hispanic or Latino (vs other) (117) *Asian, Native Hawaiian/ Pacific Islander, not available	had improvement in the BILAG score at Week 24. There was no significant difference between placebo and treatment groups when it came to viral or other infectious AE. Most commonly reported AEs were urinary tract infections, upper respiratory infection, and headaches	arms. In subgroup analysis of ISM high and ISM low, ISM low were more responsive to Rontalizumab at week 24.	IFIT1, MX1, OAS1, OAS2 and OAS3). Response to Rontalizumab was seen in ISM-low subpopulation which accounts for 24% of overall sample size rather than the ISM-high subgroup.	
Sifalimumab (MEDI 545)	A fully human IgG1K Mab antibody that binds to multiple IFN-α subtypes	NCT00299819	Ia	Total: 69 patients (96% Female) • 34 patients treated with Sifalimumab • 17 patients on placebo • 18 patients' part of open-label phase	• 78% Caucasian • 22% Not reported	AE rates per subject were similar among all groups, infection rates did not differ significantly between treatment and placebo arms	PK analysis showed that sifalimumab is dose proportional across the dose range studied and has a half-life of 15–24 days. With regards to immunogenicity, all subjects tested negative for anti-sifalimumab. Adjusted mean SLEDAI scores showed a statistically significant improvement in disease activity in sifalimumab patients at study day 56, and sifalimumab patients were less likely to exhibit a BILAG flare.	Sifalimumab neutralized overexpression of type I IFN signature in subjects with SLE. PD analysis showed that elevated baseline IFN signature (36/62) experienced a dose-dependent inhibition of the IFN signature.	[32]

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		NCT01283139	IIb	Total: 431Patients (92% female) • 108 on placebo • 323 receiving Sifalimumab	• 58.7% White (253) • 14.8% Asian (64) • 7.7% Black (33) • 4.6% American Indian/ Alaskan Native (20) • 13.9% Other (60) • 63% Ethnicity non-Hispanic (271)	The primary endpoint was met after 52 weeks – more patients on sifalimumab achieved an SRI-4, and the sifalimumab group had greater improvement in skin measured by the CLASI Adverse events occurred at similar frequencies within both groups with the exception of Herpes Zoster infections, which were more common in the Sifalimumab group	Secondary efficacy measures, assessed at week 52, showed that Sifalimumab receiving patients experienced greater improvement in CLASI with maximum improvement seen after 20–24 weeks. The percentage of patients receiving oral corticosteroid of >10mg/day at baseline and who tapered was low. Although more patients on sifalimumab 600 mg and 1200 mg met the criteria for tapering compared to placebo.	Interferon gene signature test was based on the expression of 4 interferon regulated genes (IFI27, IFI44, IFI44L, and RSAD2). High IFN gene signature subgroup analysis of SRI (4), mSRI (8) and BICLA showed that those on sifalimumab experienced substantial improvements in comparison to those on placebo.	[36]
Anifrolumab (MEDI 546)	A fully human IgG1K Mab directed against the type I Interferon Receptor which blocks signaling of all type I IFNs through the receptor	NCT02601625	I	Total: 30 patients (37% female) • 12 patients on placebo • 18 receiving Anifrolumab	• 30% White (9) • 63.3% Black or African-American (19) • 6.6% Other* (2) *Native Hawaiian or other Pacific Islander or Asian	Adverse events were reported by 50% of patients receiving Anifrolumab and 33% of patients on placebo. Most common AEs reported in the Anifrolumab group were upper respiratory tract infections and dry throat.	The SC administration of Anifrolumab 300-mg and 600-mg reached peak serum concentration (T_{max}) 4 to 7 days after injection and was consistent with the pK of SC administered antibody. All subjects had quantifiable serum Anifrolumab concentrations for approximately 28 days after dose.	The IFN gene signature in healthy volunteers is relatively low.	[48]
		NCT01438489	IIb	Total: 305 patients (93% Female)	• 41.7% White (127)	The SRI-4 response with sustained	In the modified ITT population, 25.5% of the	Greater efficacy was observed in all the	[49]

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				• 102 received placebo • 99 received Anifrolumab 300 mg • 104 received Anifrolumab 1,000 mg	• 13.4% African American (41) • 7.2% Asian (22) • 1.6% American Indian/ Alaskan Native (5) • 30% Other (110) • 58% Ethnicity, non-Hispanic (177)	reduction of oral corticosteroids at week 24 was analyzed in the modified ITT population and IFN-high subpopulation (75% of patients). A Cochran-Armitage trend test showed that patients on Anifrolumab was greater than placebo in the modified ITT group and in the IFN-high subpopulation. In the modified ITT group, 34.3% of Anifrolumab 300 mg patients and 28.8% of Anifrolumab 1000 mg achieved a response. Response rates in the IFN-high population was observed to be 36% for Anifrolumab 300 mg and 28.2% for Anifrolumab 1000 mg in comparison to the 13.2% receiving placebo.	placebo group achieved SRI(4) response with a sustained reduction of oral corticosteroids at week 52, compared with 51.5% in the anifrolumab 300 mg group and 38.5% in the anifrolumab 1000 mg group. Anifrolumab receiving patients were observed to have significant rates of improvement across a broad range of composite and organ-specific measures. Anifrolumab treatment was well-tolerated and adverse events reported were similar across the anifrolumab and placebo group. Herpes zoster infections were reported in 5.1% of patients receiving 300 mg of anifrolumab and 9.5% of patients receiving 1000 mg of anifrolumab.	endpoints in patients with a high baseline IFN gene signature. However, this interpretation may be limited by its small size, as 75% of participants were high IFN.	
		NCT02446912	III	Total: 457 patients (92% Female) • 180 received Anifrolumab 300 mg	Not Available	The primary endpoint was not reached as there was no difference in the SRI (4)	Secondary outcomes including BICLA response were met. 46.1% (83/180) of	Anifrolumab 300 mg suppressed interferon gene signature in comparison to	[66]

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Type I Interferon Antagonist	Mechanism of Action	NCT Identifier	Study Phase	Sample Size	Race and Ethnicity	Primary Outcome	Secondary Outcome	Genes and effect on IFN signature	References
				• 93 received Anifrolumab 150 mg • 184 received placebo		response at week 52. Patients on Anifrolumab 300 mg vs placebo respectively had a 36.2% (65/180) and 40.4% (74/184) response rate. SRI (4) rates in the Interferon gene signature high subgroup were 35.9% response rate in Anifrolumab 300 mg and 39.3% in placebo.	subjects in the Anifrolumab 300 mg showed difference in the BICLA in comparison to placebo 29.6% (54/184). In the high interferon gene signature subgroup, BICLA difference occurred 45.9% (68/148) Anifrolumab vs 27.5% (41/151) placebo.	placebo. Serologic changes in individuals on Anifrolumab 300 mg showed trends toward normalization.	
		NCT02446899	III	Total: 362 patients (93% female) • 180 received Anifrolumab • 182 received placebo	• 60% White (217) • 11.6% Black (42) • 16.6% Asian (60) • 11.9% Other or missing data (43) • 30% Hispanic or Latino ethnic group (108)	The study met the primary BICLA endpoint. At week 52, a BICLA response occurred in 86 of the 180 patients receiving Anifrolumab and 57 of 182 receiving placebo; 47.8% and 31.5%, respectively.	Secondary endpoints such as glucocorticoid dose and severity of skin disease showed a significant benefit. Sustained prednisone reduction of 7.5 mg or less from baseline (170 of 362 received corticosteroid, 47% overall) corticosteroid dose of 10 mg or more was seen in 51.5% (45 of 87) of patients receiving Anifrolumab and 30.2% (25 of 83) receiving placebo.	Subpopulation analysis showed that 48% of those Anifrolumab receiving and 30.7% of placebo patients with a high interferon signature (301 out of 362 patients, 83.1%) experienced a BICLA response at week 52. Meanwhile a BICLA response was seen in patients receiving Anifrolumab 46.7% and placebo receiving patients 35.5% in the low interferon signature group (16.7% of	[54]

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								overall patients) experienced.	