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Advances in Interferon-alpha targeting-approaches for Systemic Lupus Erythematosus treatment

Running title:

Interferon-alpha targeting in SLE

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Summary

Conventional therapies seem to have reached the limit of their ability to treat patients with Systemic Lupus Erythematosus (SLE). To improve the outcome for these patients, new drugs are needed. Several attempts have been made to introduce targeted therapies for this complex disease. One of these targets is Interferon (IFN) alpha, whose production is increased in SLE, contributing to its pathogenesis. In this review we consider some recent advances in IFN alpha targeting-approaches.

Three monoclonal antibodies (mAbs) against several IFN alpha subtypes have been tested in phase I and II trials, showing an acceptable safety profile and promising results in terms of reducing the IFN signature and disease activity. A mAb specific for the IFN alpha receptor and active immunization against IFN alpha are also being tested. Further trials will be essential to ascertain the safety and efficacy of all these approaches.

1. Introduction

Systemic Lupus Erythematosus (SLE) is a challenging autoimmune rheumatic disease. Its aetiology is multifactorial with evidence of genetic susceptibility, environmental triggers and disturbances in both innate and adaptive immunity [1]. The outcome for patients with SLE has improved considerably in the past 60 years. However, the 15-year survival is approximately 85% and, as most SLE patients develop the disease under 45 years of age, the mortality and morbidity figures remain unsatisfactory [2].

We have published an analysis of our experience in managing Lupus nephritis over the past 30 years [3], which suggests that we have reached the optimal capacity of steroids and conventional immunosuppressive drugs to treat our patients. Unfortunately the major advances in the treatment of Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis that have been brought about by the introduction of targeted therapies, have not been replicated, to date, in patients with SLE.

Several attempts have, however, been made to introduce therapies directed at specific targets in Lupus patients. The first of these, rituximab, which blocks the CD20 molecule, is

widely regarded as being useful in treating SLE but failed to meet its endpoints in two major clinical trials [4,5]. It appears that another major trial involving a B-cell blocking drug, epratuzumab (which binds the CD22 molecule) has not met its endpoints though full results have not yet been published. Belimumab, which blocks BAFF, a B-cell activator factor, has been shown to be effective in SLE patients, particularly in those with joint and skin disease [6] and is approved by the Federal Drug Administration in the United States of America and by the European Medicines Agency. However it does not act rapidly and we do not yet have evidence of its effectiveness in treating the other aspects of SLE, such as nephritis (results from an ongoing trial are awaited) and neuropsychiatric involvement. Atacicept, which blocks two B-cell activating factors, BAFF and APRIL, has shown some benefit in preventing lupus flares [7] but whether it is effective in treating active disease is not yet known. In addition to these approaches, attempts have been made to block Interferon (IFN) alpha in patients with Lupus.

1.1 IFN alpha

Interferons (IFNs) are glycoproteins produced by nucleated cells in response to pathogens, such as viruses. They are named in reference to their ability to interfere with viral infection [8].

There are three families of interferons, namely type I interferon family (IFN I), which includes IFN alpha, beta, epsilon, kappa and omega; type II interferon termed IFN gamma; and the most recently discovered type III interferons, comprising IFN delta 1 (or Interleukin (IL)-29), IFN delta 2 (or IL-28A) and IFN delta 3 (or IL-28B) [9].

IFN alpha is a group of homologous proteins encoded by 13 different genes on chromosome 9p. All IFN I molecules bind to a single receptor, the IFN alpha receptor (IFNAR), which has two subunits (IFNAR1 and IFNAR2), and is expressed in virtually all tissues. Although most nucleated cells can produce IFN I when appropriately stimulated, plasmacytoid dendritic cells (pDCs) are the most abundant producers of IFN alpha, on a *per cell* basis [9-11].

IFN I is constitutively expressed at low levels. Following a viral infection, viral nucleic acids bind two intracellular systems: the Toll-like receptor (TLR) interferon-inducing system

(namely TLR7/8 and TLR9, which recognize RNA and DNA, respectively) present in the endosomes of monocytes, macrophages and DCs; and a cytosolic system which comprises several pathogen-recognition receptors that are ubiquitously expressed. This triggers a cascade of events that results in phosphorylation of an interferon regulatory factor which then translocates to the nucleus and causes rapid and potent transcription of IFN alpha. After its extracellular release, IFN alpha binds to the membrane-bound IFNAR, causing the activation of several signalling pathways, particularly the Janus kinases (JAK) and signal transducers and activators of transcription (STAT) pathways [8-10]. This activation results in the expression of IFN regulated genes, inducing an antiviral state in cells by suppressing mechanisms for viral replication; triggering apoptosis in virally infected cells; promoting natural killer cell-mediated and CD8+ T-cell mediated cytotoxicity; promoting the transition from innate to acquired immunity by augmenting dendritic cell (DC) maturation, cross-presentation of antigens and migration; enhancing T-helper type 1 responses, generation of T follicular helper cells, and the humoral responses [9].

Research has shown IFN I is not just a group of antiviral peptides (used in the treatment of chronic viral infections by hepatitis B and C virus), but actually a group of pleiotropic cytokines, with antitumor and immunoregulatory functions. IFN I has also been used in the treatment of malignancies and multiple sclerosis [9].

However, besides these beneficial effects in some infections, malignancies and autoimmune/inflammatory diseases, there is evidence that, paradoxically, depending on the context, IFN I can be detrimental for the host by promoting autoimmunity and inflammation [9]. In fact, several studies suggest a role for IFN I in the pathogenesis of SLE, Myositis and Systemic Sclerosis [12-14].

1.2 IFN alpha and SLE

The association of IFN alpha with SLE was discovered around three decades ago, when increased levels of this protein were found in sera of SLE patients [11]. Animal models of Lupus have also supported this association [15].

A possible causative relation between IFN alpha and SLE was suggested by the observation that IFN alpha pharmacotherapy for chronic viral infections or malignancies could lead to the development of antinuclear antibodies (inducing anti-dsDNA antibodies) and SLE [8,11,16]. Subsequently, transcriptome analyses have reported the up-regulation of multiple IFN alpha dependent genes in peripheral blood mononuclear cells from SLE patients, which is known as the IFN signature. As there is an overlap in the genes that type I and type II IFNs control, it can be difficult to distinguish between the signatures of IFN alpha, beta or gamma [8]. This IFN signature has been identified in almost all paediatric SLE patients and in about 50 to 80 % of adult patients [8]. It provides a pharmacodynamic marker to assess the activity of anti-IFN alpha therapy in vivo [8].

Although the expression levels of IFN-regulated genes have correlated with SLE severity in cross-sectional studies, longitudinal studies have not linked disease activity with individual patient levels [8,11].

The cause for the increased IFN alpha production in SLE remains uncertain [8]. Increased apoptosis and tissue damage combined with decreased clearance of apoptotic bodies may cause an increased load of immunogenic particles containing endogenous nucleic acids. Circulating anti-nucleic acids autoantibodies (such as anti-dsDNA) form immune complexes with these particles, which are then endocytosed by pDCs through the Fc gamma receptor IIa (FcγRIIa), activate TLR7 and TLR9, and cause the triggering of IFN alpha production [8,9,11]. Neutrophils and antimicrobial autoantibodies trapped in immune complexes can also induce the production of IFN alpha by pDCs [8,11]. Recently, neutrophils have gained attention as another important source of IFN alpha [8,17]. Finally, there may be a genetic contribution to the increased or sustained secretion of IFN alpha. In fact, several genetic polymorphisms implicated in the IFN I pathway have been associated with SLE [8,11].

There are multiple mechanisms associated with the pathogenic role of IFN alpha in the context of SLE. IFN alpha may facilitate humoral autoimmunity by generating T-follicular helper cells that are effective in activating B cells and antibody production. It may also enhance BAFF expression, B cell differentiation, Ig class-switching, and the survival of autoimmune B

cells. Other possible mechanisms include the inhibition of the T regulatory cell immunosuppressive activity; activation of immature DCs, breaking peripheral tolerance to self-antigens; promotion of T-helper type 1 (Th1) differentiation; promotion of cytotoxicity mediated by natural killer and CD8+ cells; inducing production of chemokines that facilitate migration of inflammatory cells into target tissues; and priming myeloid cells for enhanced responses to inflammatory stimuli [9,11]. IFN alpha also affects the vasculature and is associated with atherosclerosis in SLE patients [8,11].

2. IFN alpha targeting approaches

Given the pathogenic role of IFN alpha in SLE, agents that target its pathway are currently in development for the treatment of this disease.

2.1 Anti-IFN alpha antibodies

Sifalimumab

Sifalimumab (MEDI-545), developed by AstraZeneca/MedImmune, is a fully human monoclonal antibody (mAb) that binds to multiple IFN alpha sub-types and inhibits their actions [10,18]. It has been tested in both phase I and II trials.

A phase Ia multicentre, randomised study was conducted in adults with mildly to moderately active SLE, with a mean Safety of Estrogens in Lupus Erythematosus: National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score around 5 [19,20]. Subjects received one intravenous (IV) dose of sifalimumab (n=33 blinded phase, 0.3, 1, 3, 10 or 30 mg/kg; n=17 open-label, 1, 3, 10 or 30 mg/kg) or placebo (n=17). Adverse events (AEs) were similar between groups and no increase in infections or reactivation was observed [19]. The investigators observed specific and dose-dependent inhibition of the IFN signature and related proteins in the whole blood and skin lesions from SLE patients [19,20].

The safety and tolerability of multiple intravenous doses of sifalimumab were then confirmed in a phase Ib trial, in patients with moderate-to-severe SLE (SELENA-SLEDAI ≥6 or

a British Isles Lupus Assessment Group (BILAG) score of at least one A or two Bs). Subjects were randomized to receive IV sifalimumab (n=121: 0.3, 1.0, 3.0, or 10.0 mg/kg) or placebo (n=40) every 2 weeks to week 26, then followed up for more 24 weeks [21]. There was no difference in the frequency of serious adverse events (SAEs) between placebo and sifalimumab groups. Viral infections were more frequent in the combined sifalimumab group. Five deaths occurred, one in the placebo group and four in the sifalimumab 10 mg/Kg group. Inhibition of IFN signature by sifalimumab was incomplete in these patients with moderate-to-severe active SLE, which may reflect the contribution of other subtypes of type I IFN (sifalimumab does not inhibit beta and delta IFNs, as well as some subtypes of IFN alpha) [21]. Alternatively, it may also suggest that this signature is driven by type II or III IFNs [8,22,23]. Immunogenicity was also evaluated and, although 24% of patients receiving sifalimumab had antisifalimumab antibodies, there was no impact on sifalimumab pharmacokinetics [21].

A study on the population pharmacokinetics of sifalimumab evaluated fixed versus body weight – based regimens and demonstrated the viability of switching to fixed doses in phase IIb clinical trials [24].

Subsequently, a phase IIb randomized, double-blind, placebo-controlled study in adults with seropositive moderate-to-severe SLE (minimum disease activity for entry: SLEDAI-2K $\geq$6 and 1 BILAG A or 2 Bs and physician's global assessment $\geq$1) was carried out and the results were presented at the 2014 American College of Rheumatology (ACR) annual meeting [25]. Subjects (n=431) were randomized (1:1:1:1) to receive monthly IV sifalimumab 200, 600, 1200 mg or placebo, for one year. Randomization was stratified by disease activity, IFN signature, and geographic region. The primary efficacy endpoint, which was the presence of an SLE Responder Index (SRI) – 4 at day 365, was achieved.

The SRI is a composite index which was developed for the trials of belimumab in SLE [26]. It is defined as a $\geq$ 4-point reduction in SELENA-SLEDAI score, with no new BILAG A or no more than 1 new BILAG B domain score, and no deterioration from baseline in the physician's global assessment by $\geq$ 0.3 points. In this sifalimumab trial, the percentage of patients with a SRI – 4 response was 58.3%, 56.5% and 59.8% for sifalimumab 200, 600 and

1200 mg, respectively, versus 45.4% for placebo (effect size 1200mg versus placebo 14.4%, p=0.031). Analyses of more stringent SRI (6–8) endpoints demonstrated even greater discrimination between the 1200 mg dose and placebo. There were also significant improvements in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), joint counts and Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue scores. Baseline low complement levels and elevated anti-dsDNA levels did not normalize over time. According to the abstract presented, reported AEs were similar across groups, except for Herpes zoster which occurred more frequently in sifalimumab groups (200 mg, 4.6%; 600 mg, 3.7%; 1200 mg, 8.4%) versus placebo (0.9%) [25]; the full report of this study is awaited.

Geographic differences were assessed, in this worldwide phase IIb study, as potential confounders of efficacy [27]. Data was grouped into two regions: Region 1: high expected response to standard of care (SOC) Central America, South America, Eastern Europe, Asia; Region 2: low expected SOC response North America, Western Europe, South Africa. Greater response rates were observed in Region 1 than in Region 2. The authors suggest these results may be reflective of different baseline characteristics between populations or differences in SOC [27].

Subcutaneous (SC) administration of sifalimumab was also tested in phase II studies [28,29]. The safety profile of multiple SC doses of sifalimumab was assessed in a multicenter, randomized, double-blind, placebo-controlled study with 87 SLE patients [28]. It showed no major differences comparing to placebo. Also, an inhibition of IFN I signature by SC sifalimumab was observed in whole blood. The pharmacokinetic and pharmacodynamic effect of SC sifalimumab was also assessed in two open label trials with Japanese patients and showed the expected mechanism of action in SLE [29].

Rontalizumab

Rontalizumab (RG-7415), developed by Roche/Genentech, is a humanized mAb that inhibits at least seven IFN alpha sub-types [8,10,11]. It has also been tested in both phase I and II trials.

The safety and pharmacodynamics of rontalizumab was assessed in a phase I placebo-controlled, double-blind, dose-escalation study [30]. Patients with mildly active (mean SELENA-SLEDAI=3.4) seropositive SLE (n=60; ratio of 4:1 for active treatment to placebo) were enrolled into dose groups ranging from 0.3 to 10 mg/kg, administered via IV or SC routes. Rontalizumab was generally well tolerated and none of the AEs that occurred led to discontinuation of the study drug. Exposure-adjusted rate of infections was similar between groups. Although the proportion of reported SAEs was higher in the rontalizumab group (8.3 versus 14.6%), none of these SAEs were considered to be related to the study drug. One case of malignancy (acute myelogenous leukemia) was reported in a patient in the 3 mg/kg SC cohort. A decline in IFN signature was observed following treatment with the higher IV doses, however, none of the patients reached the levels seen in healthy individuals. Furthermore, autoantibody levels did not decline following administration of rontalizumab. It is likely that these autoantibodies are derived, at least in part, from long-lived plasma cells, and longer treatment periods may be required [30].

In a phase II study, the efficacy and safety of rontalizumab was studied in patients with moderate-to-severe active SLE (at least 1 BILAG A or 2 Bs) [31]. Exclusion criteria included active lupus nephritis and unstable neuropsychiatric lupus. Patients (n=238) were randomised (2:1) into two sequential cohorts to receive 750 mg IV rontalizumab every 4 weeks (n=81) or placebo (n=41) (Part 1), and 300 mg subcutaneous rontalizumab every 2 weeks (n=78) or placebo (n=38) (Part 2). Immunosuppressants were discontinued at randomisation and steroids were tapered to ≤10 mg/day by week 6 after randomisation. Both Part 1 and 2 lasted 24 weeks and were followed by an open-label safety extension study – Part 3 (up to 144 weeks). Neither the primary and secondary efficacy end points (reduction in BILAG-2004 and SRI, respectively, at Week 24) were met. However, in an exploratory analysis, rontalizumab treatment was associated with improvements in disease activity (SRI response), reduced flares (SELENA-SLEDAI) and decreased steroid use within a subpopulation who had a low IFN signature at the baseline. The authors suggest the lack of response in patients with high IFN signature could be due to inadequacy of dose or complex multipathway disease in that subpopulation [31]. The

incidence of reported AEs, SAEs and infectious AEs were comparable between the placebo and rontalizumab groups. Nausea was more common in the rontalizumab group (8% versus 4%). Four placebo and six rontalizumab patients discontinued study drug due to an AE (5.1% and 3.8% respectively). There were two deaths during the open label extension but they were attributed to complications of SLE. One malignancy was reported in the placebo IV group. The rate of SLE flares that were SAEs (defined according to the revised SELENA-SLEDAI Flare Index (SFI-R) instrument) was higher in the rontalizumab (6%) compared with placebo (1%) groups. All of these flare SAEs occurred in patients with high IFN signature. Antibodies against rontalizumab were identified in 3% of patients, but had no apparent impact on pharmacokinetics or safety [31].

AGS-009

AGS-009 (Argos Therapeutics) is a humanized mAb which neutralizes several IFN alpha subtypes. Its safety was evaluated in a multicenter, randomized, double blind, placebo-controlled, phase Ia single dose escalation study [32] and the results were presented at the 2012 European League Against Rheumatism (EULAR) Congress as a poster. Twenty five patients with mild-to-moderate (mean SLEDAI=4.1) seropositive SLE were randomized in 3:1 ratio within each cohort to receive a single IV dose of AGS-009 (0.01, 0.1, 0.6, 3, 10 or 30 mg/kg) or placebo in combination with standard of care. This mAb showed to be safe and well tolerated at each dose level. It resulted in significant neutralization of IFN signature at doses above 0.6 mg/Kg [32].

Despite these promising results, no more data have yet been published about AGS-009.

2.2 Anti-IFN alpha receptor antibodies

Anifrolumab

Anifrolumab (MEDI-546), developed by AstraZeneca/MedImmune, is a mAb specific for IFNAR1. The results of a phase II, open label, dose escalation study in 17 Japanese SLE patients were presented at the 2014 ACR annual meeting [29]. Patients were randomized to

receive 100, 300 or 1000 mg of IV anifrolumab, administered every four weeks. Blood samples for assessment of pharmacokinetics and pharmacodynamics were collected at multiple time points until day 169. Anifrolumab showed nonlinear pharmacokinetics. Its administration resulted in an increased and more sustained suppression of IFN signature, compared to sifalimumab. There were no major safety issues, however, this small open label study does not allow an adequate characterization of anifrolumab's safety profile [29]. Larger studies are ongoing.

2.3 IFN alpha Kinoid

The IFN alpha Kinoid (IFN-K), developed by Neovacs, is a therapeutic vaccine composed of inactivated IFN alpha coupled to a carrier protein, the keyhole limpet hemocyanin. It induces the formation of anti-IFN alpha polyclonal antibodies which neutralize most or all IFN alpha subtypes but neither IFN beta nor gamma [33].

A multicenter, randomized, double-blind, placebo-controlled, phase I/II dose-escalation study [34] assessed the safety, immunogenicity and biologic effects of IFN-K in 28 seropositive SLE patients with mild-to-moderate active disease (SLEDAI-2K scores between 4 and 10). The patients were randomized to receive three or four doses of IFN-K 30 μg (n=3), 60 μg (n=6), 120 μg (n=6), 240 μg (n=6), or placebo (n=7). IFN-K was well tolerated. There were two reported SAEs, both corresponding to SLE flares. One of them occurred in a subject who received placebo and the other one in a patient who received one dose of IFN-K 240 μg. However, the investigators consider that the later is likely linked to abrupt stopping of corticosteroids. No severe infections were reported. IFN-K showed to induce anti-IFN alpha antibodies and to down-regulate IFN related genes in SLE patients with a high IFN signature at baseline. The anti-IFN alpha antibody production in patients treated with IFN-K was associated with an increase in complement C3 levels. There was, however, no significant observed effect in anti-dsDNA levels or in disease activity evaluated by SLEDAI or BILAG during the six-month follow up period, in this small group of patients [34].

3. Discussion

The generation of the IFN signature is a complex process. The phase Ib trial with sifalimumab suggested that IFN signature is more refractory to inhibition in patients with more active disease. Unexpectedly, rontalizumab was not effective in improving clinical disease activity in patients with a high IFN signature, who had higher levels of anti-dsDNA antibodies, increased consumption of complement and higher expression of antibodies against extractable nuclear antigens. These findings suggest that, in SLE patients with more active disease, several mechanisms may contribute to the expression of IFN related genes. Thus, drugs with broader targets may have a higher probability of effectiveness.

Sifalimumab, rontalizumab and AGS-9 neutralize numerous IFN alpha subtypes; however, studies suggest that some IFN alpha activity persists, which could be due to insufficient neutralization of some IFN alpha subtypes. IFN-K induces the formation of polyclonal antibodies which neutralize most or all IFN alpha subtypes, but not other types of IFN. Furthermore, it was shown to induce higher production of antibodies in the patients who have stronger IFN signature at baseline, suggesting that IFN-K can neutralize IFN alpha activity even in these patients. Anifrolumab, which inhibits the IFNAR, will, in theory, neutralize all IFN I activity, including IFN beta. Whether this will be an advantage leading to better clinical response, or a liability, leading to increased risk of adverse events, namely severe viral infections, is yet to be known.

4. Conclusion

Current evidence shows that IFN alpha is involved in the pathogenesis of SLE; therefore, it would seem logical to use drugs that block IFN alpha to treat SLE. Given that many B-cell targeting therapies have failed to meet the endpoints in the clinical trials, IFN targeting therapies may constitute valuable alternatives. As they act upstream in the pathways that lead, not only to activation of B-cells, but also to other mechanisms involved in this complex disease, it is reasonable to postulate that IFN targeting therapies will be more effective in controlling the

diverse features of SLE than B-cell targeting drugs. However, more information is required about any additional burden of adverse events. So far, they have shown acceptable short-term safety in phase I and II studies, but phase III trials will be essential to ascertain better their safety profile and clinical efficacy. Frustratingly, although an IFN alpha blocker, Sifalimumab, has reported encouraging results, another one, Rontalizumab, failed to meet its primary endpoints. The future of IFN alpha as a target for biologic drugs in the treatment of SLE thus remains under careful scrutiny.

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