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REVIEW

Anti-interferon alpha treatment in SLE

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Abstract Several studies in the last decade have highlighted the role of the type I interferon (IFN-I) pathway, and particularly interferon alpha (IFNα) in SLE pathogenesis. As a result, a multitude of potential treatments targeting IFNα have emerged in the last few years, a few of which have already completed phase II clinical trials. Some of the treatment strategies have focused on blocking IFNα or its receptor and others the plasmacytoid dendritic cell (pDC), which is the principal IFNα producing cell. In this review, we will discuss the evidence supporting a pathogenic role of IFNα and pDC in SLE, provide an update on the current status of these therapeutic strategies, and discuss the potential advantages and disadvantages of each therapeutic approach.

Contents

Abbreviations: AE, adverse event(s); ANA, antinuclear antibodies; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; BAFF, B-cell activation factor; BDCA2, blood DC antigen 2; BILAG index, British Isles Lupus Assessment Group index; CCL2, chemokine (C–C) motif ligand 2; CXCL10, chemokine (C–X–C) motif ligand 10; DC, dendritic cell; DNAseI, deoxyribonuclease I; dsDNA, double stranded DNA; FcγRIIa, Fc gamma receptor IIa, GC, glucocorticoids; GMCSF, granulocyte/macrophage colony-stimulating factor; GRIP1, glucocorticoid receptor-interacting protein 1; IFNα, interferon alpha; IFNα-K, IFNα Kinoid; IFN-I, type I interferon(s); IFNAR, IFNα receptor; Ig, immunoglobulin; IL, interleukin; ILT7, Ig-like transcript 7; IRAK, interleukin receptor associated kinase; IRF, IFN-regulatory factor; IRG, IFN-regulated genes; ISRE, IFN-stimulated response element; IV, intravenously; KLH, keyhole limpet haemocyanin; MHC, Major Histocompatibility Complex; MyD88, myeloid differentiation factor 88; mAb, monoclonal antibodies; NET, neutrophil extracellular trap; NFκB, nuclear factor kappa B; NK, natural killer; ODN, oligodeoxynucleotides; PBMC, peripheral blood mononuclear cells; PD, pharmacodynamic; pDC, plasmacytoid dendritic cell; PI3Kδ, phosphatidylinositol-3 kinase δ; RBP, RNA binding proteins; RDBPC, randomized double-blind placebo controlled; RT-qPCR, real-time quantitative polymerase chain reaction; SAE, serious adverse event (s); SC, subcutaneously; SLE, systemic lupus erythematosus; SRI, SLE response index; STAT, signal transducer and activator of transcription; Th1, T helper 1; TLR, Toll-like receptors; TNFAIP3, TNF alpha-induced protein 3; TNIP1, tumor necrosis factor α-induced protein 3-interacting protein 1; TRAF, tumor necrosis factor receptor-associated factor; TYK2, tyrosine kinase 2; UV, ultraviolet.

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1. Introduction

The association of interferon alpha (IFNα) with systemic lupus erythematosus (SLE) can be dated back to 1979, when increased levels of this cytokine were found in SLE sera [1]. In the ensuing decades it was noted that IFNα pharmacotherapy for chronic viral infections or malignancies was associated with autoantibodies to thyroid antigens, antinuclear antibodies (ANA), anti-double stranded DNA (dsDNA), and rarely with SLE itself [2,3]. Since then, an impressive number of studies have confirmed the importance of IFNα in lupus, both in animal models and in human disease and have prompted investigation of anti-IFNα therapeutic strategies. In this review, we will summarize mechanisms of IFNα activation in SLE, including its triggers and genetics, discuss immunological and clinical effects of IFNα relevant to the disease, and discuss candidate anti-IFNα therapeutic strategies in SLE.

1.1. The type I interferon (IFN-I) pathway and the plasmacytoid dendritic cell (pDC)

IFNα, comprised of 13 subtypes, belongs to the type I interferons (IFN-I) that in humans also include IFNβ, -ε, -κ, and -ω [4,5]. All IFN-I are encoded on chromosome 9p, signal through the same heterodimeric IFNα receptor (IFNAR), and have very similar effects. IFN-I is an important component of the innate immune system, especially as it relates to antiviral defense [4,5]. Plasmacytoid dendritic cells (pDCs) which constitutively express large amounts of interferon regulatory factor 7 (IRF7), are the fastest and most potent producers of IFN-I. Nevertheless, small amounts of IFN-I could be produced by most types of cells after previous priming by IFNβ (leading to induction of IRF7) which is generated in response to stimulation by Toll-like receptor 3 (TLR3) and 4 [4,6]. IFNα is probably the most important IFN-I in SLE and is mainly produced by pDC [6]. It seems that pDCs in response to tissue injury are recruited there and get activated by nucleic acids complexed with cationic peptides to produce IFN-I [7,8]. However, pDCs shortly after activation differentiate into classic dendritic cells (DC) and cease producing IFNα [6]. A distinct characteristic of pDC, as well as of B cells, is that they are dependent on TLR7 and 9 (sequestered in early endosomes) for IFNα production [4,6]. TLR7 and 9 initiate production of IFNα after binding with exogenous (i.e. viral) or endogenous nucleic acids in complexes with immunoglobulins (Ig) or in association with cationic peptides that have been internalized through receptor-mediated endocytosis. TLR7 and 9 ligation and activation facilitate binding of an adaptor protein, myeloid differentiation factor 88 (MyD88) (Fig. 1). MyD88, in turn, associates with a complex consisting of the tumor necrosis factor receptor-associated factor (TRAF) 6 and interleukin receptor associated kinase 1 (IRAK1) and 4 proteins. This cascade of events culminates in phosphorylation of the constitutively expressed in large amounts IRF7 which then translocates to the nucleus and causes rapid and potent transcription of IFNα. After its extracellular release, IFNα binds to the membrane-bound IFNAR and induces the formation of the heterotrimer: signal transducer and activator of transcription 1 (STAT1), STAT2, and IRF9. This in turn binds to a distinct DNA response element, the IFN-stimulated response element (ISRE) and activates the transcription of many IFN-regulated genes (IRG) [9] (Fig. 1).

1.2. Triggers of IFNα production in SLE

The pivotal observation by Lars Ronnblom and his group that SLE sera can induce IFNα production by peripheral blood mononuclear cells (PBMC) of healthy donors has opened the way to our current understanding of IFNα production in SLE. These investigators attributed this activity in SLE sera to the presence of Ig and nucleic acid complexes [10,11]. In SLE, loss of self-tolerance and the resulting circulating autoantibodies prompt the formation of immune complexes with endogenous DNA or RNA-containing antigens, likely originating from apoptotic or necrotic cells. These immune complexes are endocytosed by pDCs through the Fc gamma receptor IIa (FcγRIIa) receptor, activate TLR7 and TLR9, and thus trigger IFNα and proinflammatory cytokine expression [12,13] (Fig. 1). Although FcγRIIa facilitates this interferogenic effect, C1q blocks it [14]. Of note, platelets activated by immune complexes may also trigger IFNα generation by pDC via CD154-CD40 ligation [15]. Autoantibodies associated with IFNα production in SLE include anti-dsDNA, as well as anti-RNA binding proteins (anti-RBP) such as anti-Ro, and anti-RNP [16,17].

The required excess of necrotic and apoptotic cell material for IFNα induction in SLE is generated mainly because of

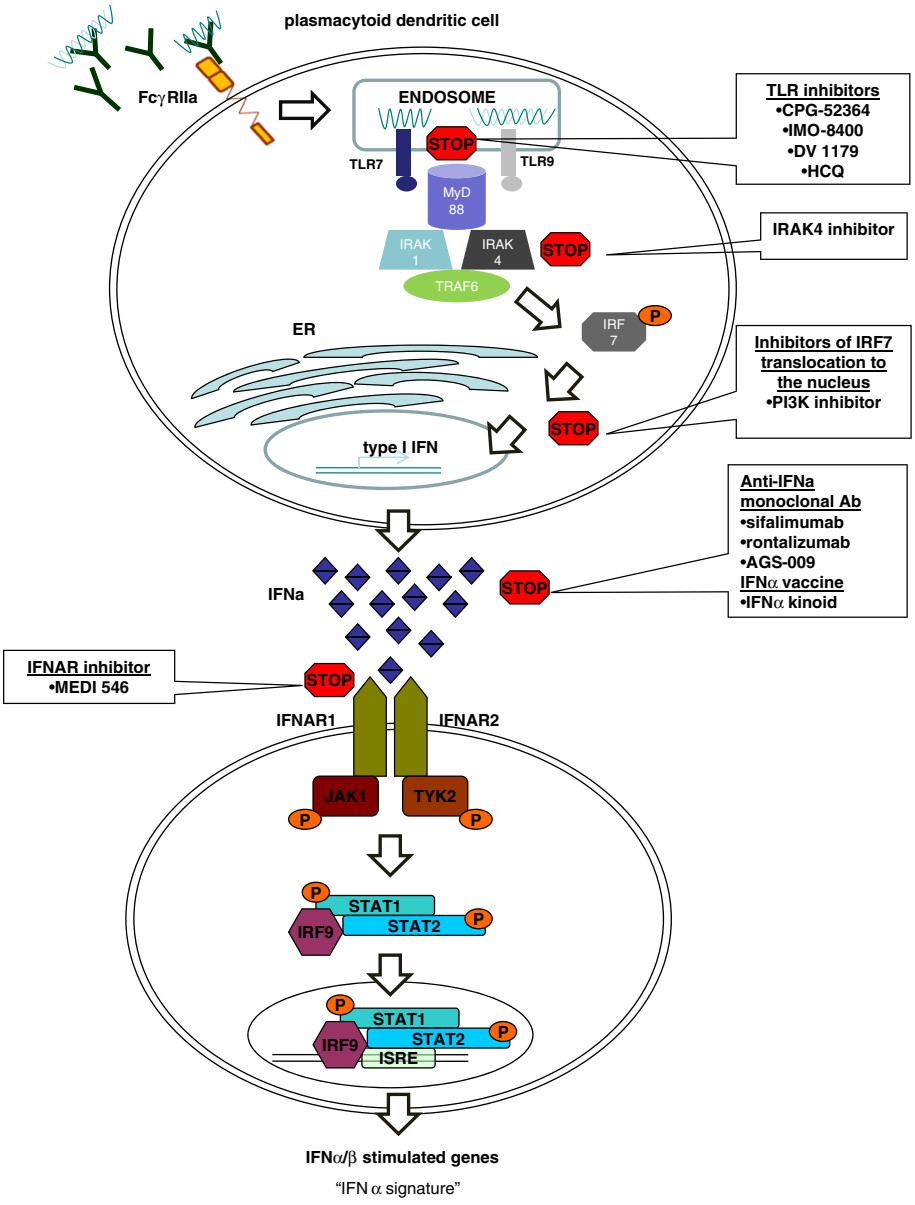

Figure 1 Type I IFN pathway. Potential targets of anti-IFNα treatments. Autoimmune complexes containing nucleic acids are endocytosed via the FcγRIIa receptor of pDCs. Inside the endosomes, RNA binds to TLR7 and DNA to TLR9 causing a conformational change of these receptors that allows anchoring of MyD88. The latter associates with TRAF6, IRAK 1 and IRAK 4. This complex leads to phosphorylation of IRF7, which then translocates to the nucleus and induces transcription of IFN-I genes (primarily IFNα). Subsequently, type I IFN binds to IFNAR, which phosphorylates JAK1 and TYK2 kinases. This culminates into the formation of a heterotrimer consisting of STAT1, STAT2 and IRF9. The heterotrimer then translocates to the nucleus and recognizes an IFN-stimulated response element that activates the transcription of many IRG. Potential inhibitors of the pathway at different levels are shown in text boxes (see text for explanations).

defects in their disposal. Additional causes for excess formation of apoptotic and necrotic cells may be exposure of keratinocytes to ultraviolet (UV) light, exposure to viral infection, or IFNα itself. More recently, a new form of cell death has been described for neutrophils whereby these cells sacrifice by extruding their nuclear material, in order to immobilize and kill invading bacteria and fungi. This nuclear material of a chromatin network full of cationic antimicrobial peptides is called neutrophil extracellular trap (NET) and the cell death NETosis [18]. Of note, some SLE patients cannot efficiently degrade NETs, probably due to inhibitors of deoxyribonuclease I (DNAseI) or anti-NET antibodies and this defect is associated with lupus nephritis [19]. NETs are also able to stimulate pDC to produce IFNα [20,21].

1.3. Genetic predisposition to SLE through increased levels of IFNα

Serum IFNα activity has been noted to be a heritable risk factor for SLE with evidence for high levels in healthy first-degree relatives of SLE patients and without discrimination among

various ethnic backgrounds [22]. These findings imply a genetic tendency towards a higher IFNα activity that may increase susceptibility to the disease. In fact, several genes implicated in the IFN-I pathway have been found to associate with SLE [9]. Both IRF5 and 7 have been associated with SLE and high levels of IFNα, but only in the presence of anti-RBP or anti-dsDNA antibodies [23,24]. In addition, polymorphisms in tyrosine kinase 2(TYK2), TLR7, TLR 8, TLR 9, IRAK1, IRF8, TNF alpha-induced protein 3 (TNFAIP3), tumor necrosis factor α-induced protein 3-interacting protein 1 (TNIP1), STAT4, osteopontin, as well as other genes, all of which are significant signaling components in the IFN-I pathway, have been associated with SLE [25–29]. Of interest, STAT4 risk loci either increase sensitivity to IFNα or its serum levels in an additive effect with IRF5 risk alleles [27,28].

1.4. The role of IFNα and pDC in SLE pathogenesis

An important role for IFNα in SLE is supported by a large number of gene expression studies showing activation of the IFN-I pathway in the disease [30–33]. In cross-sectional studies, IFN-I activation is associated with activity and severity of the disease [17,34]. However, this has not been shown in longitudinal studies [35,36]. Nevertheless, IFN-inducible chemokines, such as chemokine (C–C) motif ligand 2 (CCL2), chemokine (C–X–C) motif ligand 10 (CXCL10), and CCL19, have shown a temporal association with disease activity and could predict lupus flares in the following year [37]. In another study, high serum IFNα levels in quiescent SLE patients predicted SLE flares in the ensuing 180 days of follow-up [38]. Moreover, pharmacologic therapy with IFNα may rarely cause SLE [2,3]. The disease is often identical to idiopathic SLE and can be particularly severe [39]. In addition to the human studies, multiple studies in murine lupus have shown a strong role of IFN-I in disease pathogenesis, including murine lupus nephritis [40–43]. With regard to pDC, an important role in SLE is supported by the ability of SLE sera to induce IFNα in normal pDC, as discussed above. Furthermore, there is evidence for migration of pDC from the circulation to diseased skin and kidney in SLE patients [44–46]. Finally an inhibitor of TLR7 and 9 in the lupus-prone (NZBXNZW) F1 mice decreases autoantibody levels and ameliorates the disease [47].

There are multiple mechanisms whereby activation of the IFN-I pathway in SLE may cause disease. With regard to effects on adaptive immunity, IFNα increases the autoantigen load available to DC by increasing the NETosis of neutrophils and the apoptosis of many other cells, either directly, or indirectly via augmentation of cytotoxicity of natural killer (NK) and CD8+ T cells [4,20,48]. Furthermore, IFNα in sera from active SLE patients is able to induce differentiation of normal monocytes into DC that can capture antigens from dying cells and present them to autoreactive CD4+ T cells [49]. This occurs in part by upregulation of the major histocompatibility complex (MHC) and other co-stimulatory molecules on DC, which enhance the presentation of autoantigens to autoreactive T cells [4]. T cells activated by IFN-I are skewed towards T helper 1 (Th1) immune responses with IFNγ production, as well as generation of T-follicular helper cells that are especially good in activating B cells and antibody production [50]. IFN-I may also facilitate humoral autoimmunity by enhancing B-cell activation factor (BAFF) expression, B cell differentiation, Ig class-switching, and survival of autoimmune B cells [4,51]. Another important mechanism by which IFN-I enhances autoimmunity is the inhibition of the T regulatory cell immunosuppressive activity which is known to be defective in SLE [52,53]. Last but not least, chemokines induced by IFN-I, such as CCL2, CXCL10 are elevated in SLE and likely facilitate migration of inflammatory cells into target tissues, such as the kidney [37]. In addition to immune effects, IFNα impairs vasculogenesis in SLE and is associated with subclinical markers of cardiovascular disease [54,55].

2. IFNα blockade strategies (candidate targets along the IFN-I pathway are depicted in Fig. 1 and listed in Table 1)

2.1. Currently available agents with anti-IFN activity

There is evidence that some currently used therapeutic agents in SLE have anti-IFN activity. Specifically, glucocorticoids (GC) may inhibit IFN-I signaling in monocytes and macrophages by sequestering glucocorticoid receptor-interacting protein 1(GRIP1) [56,57]. With regard to SLE, it has been noted that GC, when used in pulse dose regimens, "extinguish" the IFN signature [17,31,58]. This effect is rapid within 1 day, but lasts less than 7 days. In contrast to pulse GC, oral GC in doses of prednisone 15–30 mg daily for 4 days, although capable in lowering the pDC number in circulation and inhibiting IFNα production in healthy donors, they are ineffective in doing the same in SLE [58,59]. The GC-resistance of pDC in SLE appears to be due to nuclear factor kappa B (NFκB) activation secondary to signaling via TLR 7 and 9 [58]. A second category of drugs with evidence for anti-IFN activity is the antimalarials which are of established clinical value in SLE. These agents which are known to inhibit acidification of endosomes, have been shown to hinder TLR9 and TLR7-mediated induction of IFNα and TNF in a recent ex vivo study [60]. Other agents of potential interest in SLE such as rapamycin and calcineurin inhibitors may also have some anti-IFN activity, but there are no relevant data in SLE [61–63].

2.2. Antibodies against IFNα or its receptor (Table 1)

2.2.1. Anti-IFNα antibodies

It is intriguing that endogenous antibodies against IFNα have been observed in SLE patients and that in some studies these were associated with decreased disease activity [64,65]. Morimoto et al. found such antibodies in 25% of 49 SLE patients and associated them with low serum IFN bioactivity and blood IFN-I signature [64]. Of note, patients with the autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED or APS1) also have anti-IFNα antibodies in association with a low blood IFN-I signature [66]. Thus an immune approach targeting IFNα appears promising. Indeed, several clinical trials have been recently initiated in SLE, either using monoclonal antibodies (mAb) against IFNα and its receptor (IFNAR), or using an active immune therapy to induce host polyclonal anti-IFNα antibodies.

Table 1 Anti-IFNα strategies in clinical development in SLE.

Agent	Type	Company	Phase of testing for SLE
anti-IFNα and anti-IFNAR strategies			
Sifalimumab	Fully human anti-IFNα IgG1 mAb	MedImmune	Phase II SC trial announced; other phase II pending
Rontalizumab	Humanized anti-IFNα IgG1 mAb	Genentech	Phase II results announced
AGS-009	Humanized anti-IFNα IgG4 mAb	Argos Therapeutics	Phase I results published
MEDI-546	Fully human anti-IFNα receptor subunit 1 (IFNAR1) mAb	MedImmune	Phase II ongoing
IFNα-Kinoid	Active immunotherapy to induce host humoral polyclonal anti-IFNα response	Neovacs	Phase I/II results published
pDC inhibitors			
CPG-52364	Selective TLR7/8/9 antagonist, quinazoline derivative	Pfizer	Phase I in healthy volunteers completed
IMO-8400	Synthetic oligonucleotide TLR7/8/9 antagonist	Idera Pharmaceuticals	Phase I trial planned
DV-1179	Bifunctional inhibitor of TLR7/9	Dynavax/GlaxoSmithKline	Phase I in healthy volunteers completed

Rontalizumab (by Genentech), is a humanized IgG1 mAb against all IFNα subtypes. The results of its phase I, randomized, double-blind, placebo controlled (RDBPC), dose escalation study have been recently published [67]. The drug was administered intravenously (IV) or subcutaneously (SC) and doses ranged from 0.3 to 10 mg/kg in 60 patients with mildly active SLE. The pharmacodynamic (PD) effects of rontalizumab were assessed by measuring [using real-time quantitative polymerase chain reaction (RT-qPCR)] the mRNA expression levels of 7 IRG representative of the IFN signature in the blood of the patients. About 50% of patients were positive for the IFN signature at baseline, as calculated from the expression levels of the 7 IRG. A rapid decline in the expression of IRG was observed in the 3 and 10 mg/kg IV-treated cohorts, could be sustained with repeated dosing and recovered in all patients, 6 months after the last dose. Median decline of IRG was dose dependent and reached 23% of baseline in the 10 mg/kg IV dose group after a single dose of the drug. IRG declines were similar in magnitude and duration in the IFN high and low groups. However, no apparent decline in the levels of IFN-inducible proteins or anti-dsDNA or anti-RBP was documented. With regard to safety and tolerability, the primary objective of the trial, the drug demonstrated an acceptable safety profile in SLE patients. Although serious adverse events (SAEs) were 14.6% in the rontalizumab group and 8.3% in the placebo-treated group, they were all classified as unrelated to the study drug. Of note, one case of acute myelogenous leukemia was recorded in the rontalizumab 3 mg/kg SC cohort. Furthermore, the results of the rontalizumab phase II trial have just been presented in an abstract form [68]. This was a RDBPC study to evaluate the efficacy and safety of the drug in 238 patients with moderate to severely active extrarenal SLE. Patients were randomized 2:1 to active drug versus placebo (n = 79). Active drug patients received 750 mg rontalizumab IV every 4 weeks (n = 81) or 300 mg SC every 2 weeks (n = 78). The study failed to achieve its primary and secondary outcome: reduction in disease activity by the British Isles Lupus Assessment Group (BILAG) and SLE response index (SRI), respectively, at 24 weeks. However, the prespecified group of patients with low IFN-I signature (24% of all patients) had significant SRI responses compared to placebo and more frequently achieved prednisone dose reduction to $\leq$10 mg daily. The IFN low and high groups were similar in disease activity. However, the IFN low group had lower rates of anti-dsDNA and anti-RBP antibodies. It is possible that the low IFN-I group improved because rontalizumab could block effectively the low levels of IFNα, whereas much larger dosages of the drug might have been required to neutralize the IFN-I signature in the high level group.

Another human IgG1κ anti-IFNα mAb, sifalimumab (by MedImmune), was evaluated in a phase I, RDBPC, single-dose, dose escalation study with an open-label extension of SLE patients with moderately active SLE [69]. There were 33 patients that received IV sifalimumab (in doses of 0.3, 1.0, 3.0, 10.0, and 30.0 mg/ml) and 17 that received placebo. Another 17 patients received open-label IV sifalimumab. The safety and tolerability of the drug, the primary outcome, was acceptable. Adverse events (AE) were similar between the active and placebo groups and serious AE were deemed unrelated to sifalimumab. No increase in viral infections or reactivations was observed. The drug caused dose-dependent inhibition of the IFN-I signature [69,70]. Additionally, the level of IFN-related proteins in affected skin was also decreased, 14 days after receiving the drug. Of interest, changes in IFN-signature in blood paralleled those in lesional skin. Furthermore, there was a trend for decreased expression of BAFF, granulocyte/macrophage colony-stimulating factor (GMCSF), interleukin 10 (IL-10), IL-1β, and TNF in both blood and skin after sifalimumab treatment [70]. An exploratory analysis of the trial showed trends towards disease activity improvement with sifalimumab compared to placebo [69]. The results of a RDBPC phase IIa trial of sifalimumab given by SC administration in 87 patients with moderate-severe active SLE have also been published in abstract form [71]. Although the drug had an acceptable safety profile and there was a 40% decrease in blood IFN-I signature in the weekly 100 mg sifalimumab arm, there was no clinical effect of the drug compared to placebo. The short duration of the trial (13 weeks) might have not allowed detection of a potential clinical benefit of the drug. Various phase II studies of sifalimumab are currently ongoing.

Argos Therapeutics has also announced the results of a RDBPC phase Ia trial of a single IV infusion of ASG-009, an anti-IFNα mAb, in 25 adults with mild to moderate SLE [72]. AGS-009 was well tolerated at all dose levels (from 0.01 to 30 mg/kg). In those patients with a positive blood IFN-I signature, assessed by RT-qPCR of 27 IRG, doses > 0.6 mg/kg resulted in significant neutralization with a dose–response trend.

Taken together these early phase clinical trials of anti-IFNa have produced hints of clinical efficacy but not yet a clearly positive signal. Unfortunately, it remains possible that this therapeutic strategy will not be successful. We are looking forward to data from larger studies in order to be able to answer this question.

2.2.2. Anti-IFNα receptor antibodies

Another approach to inhibiting the IFN-I pathway would be to block its receptor, IFNAR. Blocking IFNAR is expected to block the activity of all IFN-I types, including IFNβ. Therefore, both efficacy and toxicity might be higher compared to anti-IFNα mAbs. Currently two phase II clinical trials are underway to evaluate MEDI-546 (anti-IFNAR, subunit 1) in SLE.

2.2.3. Immunization against IFNα; IFNα Kinoid

Neovacs has championed an alternative approach to anti-IFNα treatment. Instead of mAbs, they have focused on inducing a polyclonal anti-IFNα response in SLE patients by immunizing them with recombinant human IFNα conjugated to keyhole limpet haemocyanin (KLH), the IFNα Kinoid (IFNα-K). This strategy appears to be safe as it breaks the humoral but not the cellular tolerance to IFNα, and therefore anti-IFN antibody titers are only transient, without permanently impairing host defense to viral infections [73,74]. Preclinical studies have shown that this approach is effective in a lupus flare murine model [73]. Antibodies generated could neutralize all 13 subtypes of IFNα but not IFNβ or IFNγ [74]. The generated antibodies were also shown to neutralize IFNα from sera of patients with active SLE [74]. The results of a randomized, double blind, dose escalation, phase I/II clinical trial of IFNα-K, sponsored by Neovacs, have been recently published [75]. In that study, 28 patients with mild to moderate SLE were injected with 4 doses of IFNα-K on days 0, 7, 28, and optionally on day 84. The drug had a favorable safety profile, induced anti-IFNα responses and down-regulated the expression of IRG [75]. Patients with a positive baseline IFN signature, compared to those without, had stronger anti-IFNα antibody responses and the inhibition of IRG correlated with anti-IFNα titers. Although there was no improvement in clinical indices of disease activity, c3 levels improved in patients with high anti-IFNα titers. Compared to therapies that use mAbs against IFNα, this strategy should not be limited by the induction of anti-drug antibodies.

2.2.4. Potential risks of IFNα blockade by various antibody strategies

Inhibition of IFNα may theoretically increase the risk of viral infections or reactivations and the risk of malignancy, especially in tumors linked to viral infections. As already indicated, the risk may be highest with blockade of the IFNAR, due to abrogation of all IFN-I subtypes. Although no alarm signals have been seen in clinical trials, increased vigilance is required. Patients with chronic viral or bacterial infections have been excluded from these trials, as it would be expected.

2.3. Plasmacytoid dendritic cell (pDC) inhibitors (Table 1)

The most important IFN-I implicated in SLE pathogenesis appears to be IFNα. This has been shown by quantitative and functional serum assays of IFNα in SLE patients, as well as by clinical trials that demonstrate substantial neutralization of the IFN-I signature by anti-IFNα strategies [67–69,71,72,75,76]. Although all cells can produce IFNα, the pDC is by far the most potent. Therefore a therapeutic approach that specifically targets pDC appears to be an important alternative to anti-IFN-I strategies. Since pDC largely depends on TLR7 and 9 for IFNα production, one approach to block pDC is to use short synthetic oligodeoxynucleotides (ODN) that inhibit both of those receptors. Of note, TLR7 and 9 inhibition is expected to reestablish sensitivity of pDC to the proapoptotic and IFNα blocking effects of oral GC and thus permit tapering of their dosages [58]. Furthermore, such intervention may also affect autoimmune B cells and reduce their antibody generation. Several pDC blocking strategies are in early development in SLE and include: the TLR 7/8/9 antagonists CPG-52364 and IMO-8400, as well as the TLR7/9 antagonist DV 1179 [47,77,78] (Table 1). Other approaches to block pDC might include deletion of pDC by using cytotoxic or toxin-conjugated antibodies, as well as targeting of blood DC antigen 2 (BDCA2) or Ig-like transcript 7 (ILT7), two pDC-specific receptors that can block pDC generation of IFN-I [6]. In addition, other candidate targets may include signaling downstream of TLR7/9 in pDC such as IRAK1/4 kinase, and phosphatidylinositol-3 kinase δ (PI3Kδ) [79,80].

Targeting pDC to block their IFNα production is expected to not affect the IFN-I response in other cells and therefore not compromise anti-viral defense as much as anti-IFNα strategies [6]. Of note, humans with MyD88 or IRAK4 deficiency and thus defective TLR7/9 signaling, although susceptible to some pyogenic bacterial infections early in life, were surprisingly not predisposed to viral infections [81].

3. Conclusion

There are multiple lines of evidence supporting an important role for the IFN-I pathway in the pathogenesis of SLE and thus justify the development of strategies targeting either IFN-I itself, or its generation by pDC. Clinical trials of anti-IFNα agents are at, or have completed phase II stage of development, without so far any alarming safety signals with regard to viral infection or malignancy risks. These trials have shown a significant PD effect with regard to inhibition of IFN-I signature and some promising signs in clinical efficacy, therefore supporting further development. Surprisingly, patients with low levels of IFN-I signature responded best to one of the agents in a phase II trial, a fact which may indicate that stronger inhibition may be needed for an effect in the high IFN-I signature patients. Induction of humoral polyclonal anti-IFNα responses in patients by immunization with IFNα-K is another interesting approach with encouraging safety and

PD trial results. Blockade of IFNα generation at the level of pDC is at an earlier stage of development, but may be safer, as it should not affect IFNα generation in other cell types and may have a GC-sparing effect. Although more clinical trial data are required in both treatment approaches, before we can conclude on their clinical efficacy and we fully appraise their risk/benefit ratio in SLE patients, it appears that we have made some progress in a disease with still suboptimal therapeutic options.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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