Clinical applications of IFN-α blockade in systemic lupus erythematosus

"…there is ample evidence that IFN-α is overproduced by many patients with active SLE … and may have direct effects…"

The immune system relies on a wide variety of cytokines for controlling infections, and also for dampening the inflammatory reaction in order to avoid excessive tissue damage. Among these cytokines, those of the type I interferon (IFN) family are essential mediators of antivirus defense [1]. In fact, the type I IFNs were detected as a result of their protective effects against established viruses infecting more cells. Thus, for many years, IFN-α2a and -2b have been successfully used in the therapy of chronic viral hepatitis [2]. In addition, its blockade of cell proliferation, proapoptotic effects [3] and anti-angiogenic properties have led to the use of IFN-α in melanoma patients [4]. However, under such therapy, autoimmunity is not uncommon [5,6] and viral infections associated with IFN release can lead to flares of autoimmune diseases [7]. This involvement of IFN-α in immuno–inflammatory events makes it an interesting target in rheumatology.

All type I IFNs use the same receptor, consisting of the IFN-αR1 and -R2 chains [8,9], which bind to the Janus kinases, Jak1 and Tyk2, respectively, for transducing their signals [10,11]. By contrast, IFN-γ, the single type II IFN, employs Jak1 and Jak2 for its signal transduction. While the pathway of IFN-γ ends in the phosphorylation of serine and tyrosine and subsequent nuclear localization of dimers of signal transducer and activator of transcription (STAT) 1, IFN-α mainly induces formation of a heterotrimer of STAT1 and STAT2 with IFN regulatory factor-9 [12]. In addition, IFN-α induces the phosphorylation of STAT4 dimers, which play an important role in enabling IFN-γ production [13,14], and leads to the presence of phosphorylated STAT1 dimers in macrophages [15]. These transcription factors directly lead to the various effects exerted by IFNs.

There is significant evidence that some of these effects are problematic in systemic lupus erythematosus (SLE). The therapeutic application of type I IFN, but also IFN-γ, may provoke drug-induced lupus [16,17]. Moreover, mouse model data suggest an influence of type I IFNs on lupus [18], even though IFN-γ appears to be predominant in the mouse [19]. How could this happen? There are several pieces of evidence that may help us to understand these effects. First, IFNs lead to cell death, both by preparing them for apoptosis and by stimulating killer cells. In SLE, dead cells may not be sufficiently removed [20], thus exposing the body to an overload of autoantigens [21]. Second, IFNs activate dendritic cells, which can then effectively present these autoantigens [22]. Third, IFNs may also keep autoimmune T cells alive and promote antibody production by B cells.

In contrast with their proposed role in lupus pathogenesis, type I IFNs are normally produced when cells become infected with a virus and they contribute to an effective host response. Intracellular viral RNA binds intracellular RIG I-like helicases, activating IFN regulatory factors and NF-κB [23]. Alternatively, Toll-like receptors of uninfected dendritic cells, which detect viral RNA or DNA in their endolysosomes, induce the same signaling events [24] that lead to potent type I IFN induction [25]. Indeed, in the peripheral blood, plasmacytoid dendritic cells are the main producers of IFN-α [26].

In SLE there is an abundance of immune complexes containing DNA and/or RNA. Like viruses, these immune complexes can trigger Toll-like receptors, inducing IFN-α production as well as the production of other cytokines such as TNF [27]. Along this line, there is ample evidence that IFN-α is overproduced by many patients with active SLE [28–30] and may have direct effects, as evidenced by changes in mRNA patterns [31–33] and by increased expression of STAT1, which itself is an IFN-dependent gene [34]. Thus, type I IFNs likely constitute a positive feedback loop in SLE pathogenesis,

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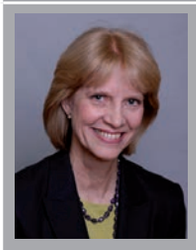

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wherein viral infection and immune complexes induce IFNs, the effects of which increase the amount of available autoantigen, foster the production of affinity-maturated autoantibodies and make IFN signaling even more effective.

Accordingly, one would expect to see beneficial effects of therapeutic interference with this feedback loop by means of blocking the type I IFN receptor or (presumably several) type I IFNs. Indeed, such an approach has been used in patients with SLE [35,36]. In a first safety trial, the anti-IFN-α monoclonal antibody MEDI-545 dampened the IFN signature in a dose-dependent way, not only in peripheral blood but also in skin samples [36]. Moreover, other proinflammatory molecules, such as TNF, were likewise down-modulated, which is consistent with the idea of interrupting a feedback loop. Compared with placebo, this approach appeared to reduce both overall SLE activity, as measured by the SLE disease activity index, and the number of SLE flares [35]. Most importantly, no obvious safety signals were reported [35].

> *"...safety will have to be monitored very carefully in longer term therapy and with particular vigilance with regard to virus infections..."*

Therefore, IFN-α blockade is being tested in controlled clinical trials in SLE [101], and given the similar lines of evidence, it will also be tested in polymyositis/dermatomyositis [37–39]. Such trials will ultimately prove or disprove this concept. However, for the time being, there is some room for educated guessing: given that subsets of patients display the classical IFN signature, one would expect these patients to be more likely to respond to IFN receptor blockade. In view of the association of type I IFN levels with disease activity, one might also argue that a type I IFN blockade would probably diminish activity rather than cure the disease. Under these circumstances, type I IFN receptor blockade may be an interesting option, along with other agents, in treating severe lupus flares or in maintaining remission following flares.

On the other hand, safety will have to be monitored very carefully in longer term therapy and with particular vigilance with regard to virus infections and even tumor surveillance. While blockade of both the type I and type II IFN systems would likely show dramatic effects in this regard [40,41], incomplete blockade of type I IFN is probably more benign. Nevertheless, both severe acute and chronic virus infections could cause problems, and it remains to be seen how much IFN blockade is feasible from this perspective.

In conclusion, the type I IFN system is a plausible target for therapeutic blockade for the treatment of severe SLE, and probably for autoimmune myositides treatment as well. Clinical trial data are still very limited, but there is hope that this concept will realize success as a feasible and effective therapy for some patients with a severe SLE flare or ongoing moderate activity associated with evidence of IFN pathway activation. Even after efficacy and safety have been secured, there is a need for a more profound understanding of the exact pathophysiological processes that involve IFNs.

Financial & competing interests disclosure

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