MINIREVIEW

Ingested Type I Interferon: State of the Art as Treatment for Autoimmunity

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We have proposed a unifying hypothesis of the etiopathogenesis of autoimmunity that defines autoimmunity as a type I interferon (IFN) immunodeficiency syndrome. We have examined toxicity and potential efficacy in three phase I (type 1 diabetes, rheumatoid arthritis, multiple sclerosis) and one phase II clinical trials in multiple sclerosis. In a phase I open-label trial in type 1 diabetes, ingested IFN-α preserved residual β-cell function in recent onset patients. In a second phase I trial, treatment of rheumatoid arthritis with ingested IFN-α reduced the secretion of interleukin (IL)-1, a pro-inflammatory cytokine. In a third phase I trial in multiple sclerosis, there was a significant decrease in peripheral blood mononuclear cell IL-2 and IFN-γ production after ingesting IFN-α. In a phase II randomized, placebo-controlled, double-blind trial in multiple sclerosis, 10,000 IU ingested IFN-α significantly decreased gadolinium enhancements compared with the placebo group at month 5. Tumor necrosis factor-α and IFN-γ cytokine secretion in the 10,000 IU group at month 5 showed a significant decrease that corresponded with the effect of ingested IFN-α on decreasing gadolinium enhancements. Ingested IFN-α was not toxic in any of these clinical trials. These studies suggest that ingested IFN-α may have a potential role in the treatment of autoimmunity. Exp Biol Med 227:981–988, 2002

Key words: autoimmunity; multiple sclerosis; type 1 diabetes; type I interferon; GALT; protein ingestion

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The Prototypic Autoimmune Diseases

We have proposed a unifying hypothesis of the etiopathogenesis of autoimmunity that defines autoimmunity as a type I interferon (IFN) immunodeficiency syndrome (1). Three major diseases, multiple sclerosis (MS), type 1 diabetes mellitus (T1DM), and rheumatoid arthritis (RA) are all thought to be autoimmune diseases characterized by T lymphocyte-delayed type hypersensitivity responses, differing in their target organs: the brain, β-islet cells, and synovium, respectively. Because the pathogenic antigen is unknown in these autoimmune diseases (2) and assuming our hypothesis is correct, supplementation with type I IFN may be a therapeutic option. Ingested type I IFN may show therapeutic efficacy (3) and have significant advantages (4). We have examined toxicity and potential efficacy in three phase I (MS, type 1 diabetes, RA), and one phase II clinical trials in MS.

MS. MS is a chronic demyelinating disease of the central nervous system, which has been postulated to be a T-cell–mediated autoimmune disease (5). MS is clinically associated with periods of disability (relapse) alternating with periods of recovery (remission), but often leads to progressive neurological disability (6). MS has been associated with abnormalities of immunoregulation (7). MS stands out as the most common and intensely investigated demyelinating human disease. In aggregate, enormous medical resources are required to manage MS. The etiology and pathogenesis of MS are still far from unraveled.

Interventions that reduce clinical activity in MS also significantly decrease enhancing lesions on brain magnetic resonance imaging (MRI) scans. Injectable (parenteral) IFN-β-1b (Betaseron, Berlax) decreases relapses by 30% and decreases enhancing lesions by 80% in relapse-remitting MS (RRMS; 8). IFN-β-1a (Avonex, Bigeu) by intramuscular injection reduces progression by 37%, relapse

rate by 18% reduction (ITT analysis), and Gd-enhancing lesions by 33% in RRMS (9). Intramuscular IFN-α2a (Roferon, Roche) treatment results in fewer new MRI lesions during the treatment period (10, 11) and fewer clinical signs of disease activity in RRMS (11). There is evidence that decreasing Gd enhancements may have a positive effect on long-term outcome in MS (12, 13). However, adverse events occur in up to 60% of patients receiving parenteral type I IFN, sometimes requiring discontinuation of treatment (9, 10, 14). The use of parenterally administered type I IFN in early RRMS is limited by the generation of interleukin (IL)-6, a potential polyclonal B cell activator (15, 16). Furthermore, 40% of IFN-β_{1b}-treated patients generated neutralizing antibodies that are frequently found in those patients who appear to lose both clinical benefits and MRI-defined responses (14).

T1DM. T1DM is a chronic disorder that results from presumed autoimmune destruction of the insulin-producing pancreatic β cells. In the United States, the prevalence of T1DM by age 20 years is 0.26% and lifetime prevalence approaches 0.40%; thus, 1.5 million Americans have T1DM (17). Histologic studies suggest that a significant reduction in the volume of β cells is required to induce symptomatic T1DM (17). Intervention at clinical onset of disease is designed to prolong the period of residual β cell function, recognized clinically as a "honeymoon" (a period in which the insulin need remains minimal and glycemic control improves, probably because of partial recovery of the insulin-producing β cell). However, when this period ends, the patient becomes completely insulin-deficient and dependent on exogenous insulin replacement. The international diabetes community agrees on the need to test potential preventive therapies for T1DM in newly diagnosed patients. Interventions prolonging the honeymoon period, indicative of the reversal of the disease, are considered positive (18). Numerous interventions have attempted to spare residual insulin activity. In the Diabetes Control and Complications Trail, experimental intense insulin therapy produced less decline in stimulated C-peptide values (19). In patients with diabetes for more than 5 years, 11% (33 of 296) of adults, compared with 0 of 75 adolescents, retained substantial insulin secretory capacity (19). Intensive, continuous insulin treatment during the first 2 weeks after the diagnosis of T1DM mellitus may improve β-cell function during the subsequent year (20). Cyclosporine (20–23), azathioprine (24), and nicotinamide did not influence the remission phase in children with newly diagnosed T1DM (25–27). The natural history of T1DM demonstrates that 90–97% of T1DM patients spontaneously end the honeymoon period within 1 year of diagnosis. In light of the above, there is no effective treatment for T1DM.

RA. RA is a common chronic disorder causing substantial morbidity in most patients and premature mortality in many (28–31). Conventional therapy for active RA includes nonsteroidal anti-inflammatory drugs followed by disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, hydroxychlororquine, sulfasalasine, or gold sodium thiomalate, but the long-term efficacy of DMARDs is less than optimal (32). Most patients cease using these drugs after 2–5 years because of toxicity or lack of efficacy (33, 34). Early control is important because patients respond best when treated early with disease-modifying therapy (35, 36). Tumor necrosis factor (TNF)-α is a critical inflammatory mediator in RA and specific cytokine blockade can be effective (37).

IL-1 levels in RA synovial fluid correlate with disease activity (38–41). IL-1 activity is detected in culture supernatants from RA synovium (42). IL-1 stimulates the release and production of matrix metalloproteinases MMP-9 but also MMP-3, which is responsible for matrix degradation (43). Dexamethasone and gold act in part by markedly downregulating spontaneous and/or cytokine stimulated production of IL-1β by peripheral mononuclear cells and synovial fluid (44).

IFN-Ingested or Otherwise. In 1957, Isaacs and Lindenmann described a factor (IFN) produced by virus infected cells with rapid antiviral activity (45). Type I IFN is composed of two homologous (50%) proteins (46) IFN-α (leucocyte IFN) and IFN-β (fibroblast IFN) with similar biological properties (47). Acid stable natural alpha interferons contain 165–166 amino acids with about 80% sequence homology to each other (48, 49). IFN-α and IFN-β are relatively similar in their actions and interact with the same cell receptor (50, 51).

The administration of cytokines via the gut offers an exciting alternative to systemic application because of the ease of dispensation in clinical use (52), patient convenience (53), ease of delivery, tolerance, and low cost along with a favorable therapeutic index (4, 54). Ingested IFN-α probably works by different mechanism than does parenterally administered type I IFN. Type I IFN are acid stable and most likely resist preprandial stomach acidity. When administered in the morning before eating, without digestive enzymes, type I IFN can survive passage to the small bowel. This is an important segment of the gut-associated lymphoid tissue (GALT), consisting of lymphoid nodules termed Peyer's patches (55), a site where regulatory cells can be generated (56, 57). Fifty to two-hundred high-affinity type I IFN receptors are found on all lymphoid cells, including those of the GALT (58, 59). Mice given oral type I IFN show a systemic neutropenia. Circulating specific antibody to IFN blocks the neutropenic effects of parenteral IFN-α, but not the neutropenic effects of oral IFN (60). Oral administration of IFN-α to mice (60), rabbits (61), dogs (62), monkeys (63), and humans (53) in doses sometimes exceeding one billion IU do not result in detectable levels of IFN-α in the blood. Up to 48 hr after 10^9 IU IFN-β was ingested by humans, neither serum IFN, β_2-microglobulin, neopterin, nor 2-5A synthetase were increased (53). If ingested IFN-α is not absorbed, how does IFN-α transduce its signal?

To examine the possible mechanism of transduction of

an IFN signal across the gut wall, we examined MxA message in lymphocytes after ingestion of IFN-α. MxA is a type 1 IFN-specific-induced mRNA/protein, thus providing a marker indicating type I IFN/type I IFN receptor interaction (64). Induction of Mx mRNA is found in the absence of detectable serum IFN activity, demonstrating that MxA gene expression is a good marker for detecting minute quantities of biologically active type I IFN (65).

Ingested type 1 IFN must act through type I IFN receptors to transduce signals to immuno-modulatory cells (50). We examined the relative levels of MxA mRNA signal using semi-quantitative reverse-transcription polymerase chain reaction on splenocytes from mice and PMNCs from humans after IFN-α ingestion. Both mice spleen cells (4-fold) and human PMNC demonstrated significant inducible levels of Mx mRNA after ingesting IFN-α. Murine whole splenocytes demonstrated upregulation of MxA mRNA after IFN-α ingestion of 10 and 100 units, clinically effective doses in EAE, but not after 1000 or 5000 units, clinically ineffective doses in experimental autoimmune encephalomyelitis (EAE; 66). Ingested IFN-α acts via established pathways of type 1 IFN signaling (67).

Clinical Studies—So far

MS. We have repeatedly and reproducibly shown that ingested IFN-α is a robust biological response modifier in EAE (66, 68–70). We determined that ingested IFN-α was nontoxic and had biological effects in humans in a phase I study. Ingested hrIFN-α showed no toxicity in normal volunteers or patients with RRMS at doses ranging from 300 to 100,000 units. In subjects with RRMS, a significant decrease in mitogen-induced peripheral blood mononuclear cells (PMNCs) proliferation and serum soluble intercellular adhesion molecule-1, a surrogate measure for disease activity in MS, was found after ingesting six doses every other day of 10,000 and 30,000 units IFN-α. IFN-α can establish a Th1-like cytokine bias in humans (71–73). The RRMS subjects also showed decreased mitogen-induced IL-2 secretion after ingesting 10,000 IU IFN-α and decreased IFN-γ, TGF-β, and IL-10 production after ingesting 30,000 IU IFN-α. The decreased secretion of IFN-γ and IL-2, Th1-like cytokines, suggests that ingested IFN-α may inhibit predominantly pro-inflammatory Th1-like T-helper cells in RRMS, a potential site of intervention at the level of effector T cells in MS. The above phase I study supported the oral use of human IFN-α as a biological response modifier in humans (74).

Subsequently, we investigated if ingested human recombinant interferon-α2a (hrIFN-α2a) was safe and if the treatment could reduce the number of gadolinium-enhanced lesions on serial cerebral MRI in patients with active RRM. Serial MRI detects 5–10 times more disease activity in RRMS and secondary progressive MS patients than is clinically apparent and consequently is a sensitive tool with which to monitor disease activity (75–80). Entry criteria included clinically definite RRMS and one or more gadolinium-enhanced lesions on a screening MRI. Eighty patients were screened, 33 found eligible, and 30 patients were enrolled for treatment, with 10 in each treatment arm. Eligible patients were randomized to treatment with placebo, 10,000 or 30,000 IU IFN-α2a ingested on alternate days for 9 months. They were evaluated clinically and with monthly cerebral MRI. Sample size projections were based on the assumption of a parenteral "IFN-like effect," a 90% reduction of enhancements evident within 1 month of the initiation of treatment in the active treatment groups sustained over the 9-month study. This was not observed. However, data analysis showed a treatment effect in the 10,000 IU group. By direct monthly comparison of placebo and 10,000 IU group in treatment month 5, there were significantly fewer enhancements in the 10,000 IU group compared with the placebo group. The cumulative mean number of enhanced lesions showed a decrease in the 10,000 IU group compared with placebo starting at 3 months and continuing until 6 months. Analysis of recall antigen tetanus toxoid-stimulated PMNCs TNF-α cytokine secretion in the 10,000 IU group showed a significant decrease compared with placebo that corresponded with the apparent effect of 10,000 IU ingested IFN-α2a on decreasing gadolinium enhancements. IFN-γ cytokine secretion showed a clear downward trend in the low dose group compared with placebo at month 5. The combined data from the phase I and II trials do not suggest a Th1-cytokine bias after ingested IFN-α. Relapses and adverse events were not different among the treatment groups. Ingested IFN-α2a did not induce systemic anti-IFN-α antibodies. These results suggest that doses lower than 10,000 IU may be necessary for clear efficacy because of tachyphylaxis or pharmacological tolerance at 10,000 IU (81).

T1DM. We previously determined that ingested murine IFN-α (mIFN-α) administered to NOD mice decreased islet inflammation and suppressed T1DM (82). Ingestion of mIFN-α increased the mitogen-induced production of IL-4, IL-10 (Th2-like cytokines), and IFN-γ secretion in spleen cells from treated mice. Adoptive transfer of unstimulated splenocytes secreting IL-4 and IL-10 from mIFN-α-fed donors suppresses spontaneous T1DM in recipients. The protective effect of adoptively transferred unstimulated splenocytes demonstrates the presence of ingested IFN-α-activated regulatory splenic cell populations that may work via increased IL-4 or IL-10 production (82). The increase of Th2-like cytokines in the NOD mouse model of T1DM is in contrast to the inhibition of Th1-like cytokines in EAE and RRMS.

Islet transplantation possesses significant potential advantages over whole-gland transplants because it is simple, may achieve insulin independence, and has clear advantages over exogenous insulin therapy. Therefore, we examined if ingested IFN-α, administered to islet allograft recipients, could prevent islet allograft rejection. Recipient C3H mice ($H\text{-}2^k$) were made diabetic and either untreated or treated with 10 to 1000 IU ingested murine IFN-α daily from day

−7 through day +14 after transplantation for a total of 21 days. Seven days after diabetes induction, recipients received allograft islets isolated from C57BL. 10 donors ($H\text{-}2^b$) under the kidney capsule and were followed for overt diabetes via elevated blood glucose. Control recipients and recipients fed 1000 IU all became diabetic by day 13, whereas mice ingesting IFN-α had delayed rejection for up to 27 (10 IU) to 29 days (100 IU) after islet transplantation. Treatment of recipients of islet allografts with ingested IFN-α doubled the time period before rejection compared with control mice. The feeding period with daily IFN-α was doubled from 21 days to 42 days in total, 7 days before transplant, and 35 days after transplant. Treatment of recipients of islet allografts with prolonged ingested IFN-α prevented rejection in 33% of recipients 35 days posttransplant. Ingested IFN-α can prevent rejection if given continuously after transplantation (83).

Because there is a historical experience of a low incidence of spontaneous remission in T1DM, interventions preserving β-cell function have been used to identify positive therapeutic outcomes. We treated 10 newly diagnosed T1DM patients with 30,000 IU ingested IFN-α within 1 month of diagnosis in an open-labeled phase I clinical trial and examined the difference between baseline and induced C-peptide responses at 0, 3, 6, 9 and 12 months. Eight of the 10 patients showed preserved β cell function with at least a 30% increase of stimulated C-peptide levels at 0, 3, 6, 9, and 12 months after initiation of treatment. There was no discernible chemical or clinical toxicity associated with ingested IFN-α. There were no detectable serum increases in Th1 cytokines in these patients after IFN therapy. Ingested IFN-α has potential to preserve residual β-cell function in recent onset T1DM (84). A phase II randomized, placebo-controlled, double-blind clinical trial is ongoing in recently diagnosed type 1 diabetes.

RA. RA is a common chronic disorder involving the synovial membranes of multiple joints that is considered by most to be an autoimmune disease. Within joints of patients with RA, chronic (lymphocyte mediated) or acute (lymphocyte and polymorph mediated) tissue inflammation is the predominant mechanism leading to tissue changes in synovial joints. In light of our findings in another autoimmune disease (MS), we performed an open-label pilot phase I study with ingested IFN-α to determine the safety, potential deleterious clinical effects on joint disease, and potential modulation of relevant pro-inflammatory cytokine secretion in RA.

Substantial amounts of IL-1 are found in RA. There is a striking correlation between levels of IL-1 in rheumatoid synovial fluid and disease activity (38, 39). Enhanced *in vitro* IL-1 generation by circulating monocytes is temporally linked to an early event in the onset of exacerbation of RA (40). IL-8, a potent chemotactic and proadhesive mediator for PMNCs, plays a key role in amplifying and perpetuating inflammation. IL-8 recruits inflammatory cells into the joint (85). IL-8 is the major t-cell chemoattractant in RA synovium (86) and is secreted by T cells (87). RA PMNCs are activated to produce proinflammatory IL-8 mRNA peripherally before entering the synovium (88). As mentioned above, TNF-α plays a major role in RA and its blockade can be effective (37).

Four patients meeting the American College of Rheumatology criteria for the diagnosis of RA were examined (89). Patients underwent a symptom-directed physical examination and complete rheumatologic examination performed at 2-week intervals including standard painful and swollen joint counts, patient and physician global assessment of disease activity and duration of morning stiffness (MS), and routine blood tests, including erythrocyte sedimentation rate (ESR). The specific endpoint was a 20% decrease in signs or symptoms of joints as defined by joint count (painful and swollen), duration of morning stiffness (MS), patient or physician global assessment of disease activity, and ESR at 8 weeks (exit) following entry into the study. Thirty thousand units of hrIFN-α were injected for 8 weeks every other day. PMNC were obtained at entry, every 2 weeks during the study, and at exit and were stimulated with OKT3 (CD3) monoclonal antibody for 2 days and measured by ELISA assay for IL-1β, IL-8, and TNF-α.

Ingested hrIFN-α was not toxic at any dose as measured by routine blood chemistries. Overall, of the 24 possible clinical and laboratory disease indices measured, there were 14 indices that improved by at least 20% and 4 that worsened by 20%, all the worsening in one patient. This suggests that ingested hrIFN-α is probably not clinically toxic in RA.

Ingested IFN-α modified biological responses in RA. Decreased PMNC CD3-induced IL-1 secretion (ng/ml) was seen after hrIFN-α ingestion in all four patients comparing entry and exit samples (#1, 948 vs 486; pt #2, 266 vs 87; pt #3, 1798 vs 1558; pt #4, 1205 vs 842). There was no increase in IL-1 secretion in any patient. Two patients also had IL-8 cytokine analysis performed on 48-hr unstimulated PMNCs. These two patients showed at least a 75% reduction in the spontaneous secretion of IL-8 secretion at exit compared with entry (CW: 39,150 pg/ml entry vs 9,840 pg/ml exit; JN: 15,850 pg/ml entry vs 1,620 pg/ml exit). There was no consistent alteration of CD3-induced secretion of TNF-α. Treatment of RA with ingested IFN-α is nontoxic and significantly reduces the secretion of IL-1, a pro-inflammatory cytokine (90).

Different cytokines are preferentially affected by ingested IFN-α in different disease states and species. In phase I and II studies in MS, IL-2, IL-10, TGF-β, TNF-α, and IFN-γ are decreased. In the NOD animal model of T1DM, IL-4 and IL-10 are increased. In RA, IL-1 is decreased. The different effects on cytokines in different disease states probably reflects the pleitropic effect of ingested IFNα in different microenvironments (91, 92).

Sjogren's syndrome. Other investigators have examined oral IFN-α in another autoimmune disease, Sjogren's syndrome (SS). A single-blinded controlled trial was

conducted to test the efficacy of low-dose oral human IFN-α to improve salivary function in patients with SS. Fifty-six outpatients with primary and four patients with secondary SS were assigned randomly into treatment groups of either IFN-α or sucralfate (non-IFN control). The IFN-α (150 IU) or control was given orally three times a day for 6 months. Saliva was quantitated monthly by the Saxon test. After 6 months of treatment, 15 of 30 (50%) IFN-α-treated patients had significantly greater saliva production increases at least 100% above baseline, compared with 1 of 30 (3.3%) control patients. Serial labial salivary gland biopsies of 9 IFN-α responder patients showed that lymphocytic infiltration was significantly decreased and the proportion of intact salivary gland tissue was significantly increased after the IFN-α treatment (93). Additional controlled trials in SS showed that the use of 150 IU IFN lozenges TID for 12 weeks in subjects with primary SS improved salivary output and decreased complaints of xerostomia without causing significant adverse medical events (94).

Low Dose by Mouth—Low Dose by Injection?

Ingested IFN-α shows an inverted U-shaped immunological and clinical dose–response curve. Immune effects circumscribe the clinical effective doses in our EAE models. Inhibition of the murine immune system occurred at 10 and 100 IU, clinically effective doses, and also at 0.1, 1 and 1000 IU, clinically ineffective doses. Ingested IFN-α significantly decreased spleen cell proliferation and IL-2 secretion at clinically ineffective low (0.1, 1 IU) and high doses (1000 IU; 66). However, mice fed 10 and 100 IU mIFN-α were protected against EAE, but animals fed 0.1, 1, and 1000 IU were not protected despite discernable immune inhibition at these lower or higher doses (66).

Mx is a type 1 IFN-specific induced mRNA/protein, thus providing a marker indicating type I IFN/type I IFN receptor interaction (64). Induction of Mx mRNA is found in the absence of detectable serum IFN activity and demonstrates that MxA gene expression is a good marker for detecting minute quantities of biologically active type I IFN (65). Murine whole splenocytes showed upregulation of Mx mRNA after IFN-α ingestion of 10 and 100 IU, clinically effective doses, but not after 0, 1000, or 5000 IU (67). High or very low ingested IFN-α doses have immune effects without a significant induction of MxA mRNA. These data show that MxA mRNA bio-induction coincides with EAE clinical effects, and inhibition of immune function such as proliferation and cytokine production can circumscribe doses showing clinical effects. In general, because of the U-shaped dose–response curve, there is decreasing (para) clinical and clinical activity with increasing doses of ingested hrIFN-α.

The failure to show persistent biological effects on MRI-monitored inflammatory disease activity in our phase II study may be secondary to tachyphylaxis or pharmacological tolerance from an excessive nonoptimal IFN-α dose. The results of the phase I study demonstrating immunomodifying effects at 10,000 and 30,000, but not after 100,000 units hrIFN-α2a suggest a U-shaped dose–response curve (74). These results and those in the Mx mRNA experiments above suggest that large quantities of ingested IFN-α may not have the same effect as lesser quantities (66).

Others have noted a loss of oral type I IFN anti-viral and anti-inflammatory activity with increasing dose, demonstrating a bell-shaped dose response curve. Oral administration of 1–10 IU type I IFN reduces early replication of murine cytomegalovirus in both the spleen and liver of murine cytomegalovirus-infected BALB/c mice, whereas doses from 50–1000 were ineffective (95). There were anti-asthmatic effects of 1–100 IU oral hIFN-β in OVA-sensitized and challenged guinea pig asthma, but this effect was lost at 1000 IU (96). Lower doses of ingested IFN-α may paradoxically provide increased therapeutic activity.

Surprisingly, parenteral IFN-α also shows a U-shaped response curve. Injection of maximal tolerated doses of IFN-α failed to inhibit angiogenesis in human bladder tumors in nude mice, whereas daily administration of lower doses gave maximal biological effects and was much more effective (97). The administration of maximal tolerated dose of IFN-α probably failed to inhibit angiogenesis due to a feedback mechanism leading to induction of suppressors of cytokine signaling (SOCS), such as STAT-induced STAT-inhibitor-1 (SSI-1) (98). The SOCS proteins are a new family of negative regulators of cytokine signal transduction. The SOCS proteins act in a negative feedback loop to suppress signal transduction from cytokine receptors. SOCS gene expression is induced by cytokines both *in vivo* and *in vitro*, and once produced, the SOCS proteins act directly on components of cytokine signaling to shut them down (99). SOCS1 and SOCS3 but not SOCS2 are inhibitors of IFN-mediated Janus-activated kinase/STAT signaling pathways (100). Thus, higher doses of IFN-α may be counterproductive if SOCS1 and SOCS3 are activated.

What's Next? The Best Dose!

Ascertaining optimal bio-immuno-clinico-activity of other lower dose(s) of ingested IFN-α2a (100–3000 IU) becomes imperative. There appears to be a correlation between MxA mRNA induction and clinical effects. On this basis, the dose that provides the maximum induction of MxA mRNA may potentially generate the greatest decrease of brain MRI T1 gadolinium enhancements in subsequent phase II MS clinical trials. The optimal dose of ingested IFN-α can be measured by examining PMNC MxA mRNA induction after ingesting 100–3000 IU IFN-α2a. The dose that provides the maximal MxA induction in the most patients can be used for the phase IIb MRI/MS clinical trial.

The first phases of clinical trials using oral administration of biological agents have begun. The goals of additional trials are optimization of dosing and clear proof of efficacy.

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