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Comparative Clinical Trial of Antibodies to Interferon-Gamma (IFN-γ) and Tumor Necrosis Factor-Alpha (TNF-α) in the Treatment of Rheumatoid Arthritis

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Abstract

In 1974, in *Nature*, one of us has proposed a radically new idea that led to the development of anticytokine therapy which is now used around the world for the treatment of autoimmune diseases. We were the first to use antibodies to IFN-γ and were some of the first to suggest using antagonists of TNF-α in the treatment of autoimmune and inflammatory diseases as well. Our method suppresses one of the main pathogenetic mechanisms of these diseases. Antibodies to IFN-γ and TNF-α exhibit dramatic effects on clinical manifestations of rheumatoid arthritis (RA). However, in our trial ultrasound assessment of the synovial membrane thickness in RA patients showed that only anti-IFN-γ exerted pronounced anti-inflammatory effect. Some patients who underwent treatment with antibodies to TNF-α developed a number of complications. Anticytokine therapy (mono- and poly-) alone or in combination with other drugs can possibly be used not only in the treatment of autoimmune diseases, but also in other pathologies with cytokine synthesis disturbances (a number of neurological, psychiatric, endocrine, and other diseases).

Keywords

Rheumatoid Arthritis, Autoimmune Diseases, Anti-Cytokine Therapy, Anti-IFN-γ, Anti-TNF-α

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1. Introduction

In 1974 one of us proposed that a disturbance in IFN synthesis can lead to the development of autoimmune diseases and that antibodies to IFN could be therapeutic [1]. In those times there were only three known types of interferon—alpha, beta, and gamma, which were later classified as cytokines. Currently there are more than 100 known cytokines including TNF-α, interleukin-6, and others. Cytokines are small molecular weight proteins, glycoproteins and peptides which, among other functions, are involved in cell signaling between immunocompetent cells. In certain cases they serve as anti-inflammatory agents while in others they stimulate inflammation, regulate certain functions of different organs and systems, and cause cell death. Cytokines are also involved in the interaction between immune, nervous, and endocrine systems. Normal functioning of the organism is determined by normal functioning of the cytokine system. Any breakdown of cytokine synthesis leads to a disease state.

In 1975 Simon Skurkovich and coworkers pioneered the field of anticytokine therapy by using antibodies to interferon-alpha (IFN-α) and later IFN-γ to treat small groups of patients with RA [2]-[4]. In 1989 he also proposed to use anti-TNF-α together with antibodies to some IFNs to treat different autoimmune diseases [5]. Later there was successful treatment of patients with RA with chimeric monoclonal antibody to TNF-α [6]. We hypothesized that autoimmune diseases may develop in organs in which a disturbance of cytokine production occurs [7]. Our pioneering role in anticytokine therapy is well recognized in the world [8].

Today a large body of evidence suggests that IFNs, especially IFN-γ, enhance autoimmune and inflammatory processes and play an important role in the pathogenesis of autoimmune diseases including RA [9]-[13]. Our pilot study in 23 patients with treatment-resistant RA using antibodies to IFN-α, IFN-γ, and TNF-α showed safety and obvious clinical benefit of antibodies to IFN-γ [3]. Later these results were confirmed in a small double-blind investigation [4].

In this report we present results of a larger randomized, double-blind, placebo-controlled trial of anti-IFN-γ and anti-TNF-α therapies administered to separate groups of patients with RA. We also present, for the first time, effect of these antibodies on the thickness of rheumatoid synovial membranes.

2. Material and Methods

Antibodies (IgG) to IFN-γ and TNF-α were produced by Advanced Biotherapy Laboratories and had a protein concentration of approximately 50 mg/ml. Final preparation passed all standard tests for safety, sterility, and endotoxin levels based on US Food and Drug Administration guidelines. Each antibody was aliquoted to vials at 2 ml/vial. Commercial human albumin with saline from an American blood bank was used as placebo. Each ampule contained 2 ml of albumin (48 - 50 mg of protein/ml). Anti-cytokines and placebo were supplied by Advanced Biotherapy Laboratories in identical vials that were indistinguishable.

Eligible patients were at least 18 years of age meeting the 1987 criteria of the American College of Rheumatology (ACR) for the diagnosis of RA, with onset of disease after 16 years of age, who had had disease for at least 6 months, had a history of failed treatment with at least one disease-modifying anti-rheumatic drug (DMARD), and had evidence of erosive disease on radiography of hands and feet. In addition, patients had to have active disease as defined by the presence of 6 or more swollen joints plus at least three of the four of the following criteria: duration of morning stiffness > 45 min; 8 or more tender joints; erythrocyte sedimentation rate (ESR) > 25 mm/h; and C-reactive protein (CRP) > 2 mg/dL.

Only patients who were admitted to the rheumatology clinic because of evident exacerbation of RA, had failed previous out-patient treatment, and had not received DMARDs for at least 3 months and intra-articular glucocorticoids (GCS) for at least 4 weeks prior to the trial entered the study. Concomitant therapy with stable doses of oral GCS (not exceeding the equivalent of 10 mg prednisolone per day) and/or NSAIDs was permitted. Intra-articular GCS were not permitted during the study.

Patients were excluded if they had clinically significant concurrent diseases, impaired renal or liver function, a history of malignant disease or serum sickness (or of other allergic reactions to foreign proteins), or marked leuko- or thrombocytopenia. Pregnant or breast-feeding women and women of child-bearing age not practicing approved methods of contraception were excluded.

Fifty-five RA patients were randomly assigned to receive anti-IFN-γ (20 patients), anti-TNF-α (20 patients), or placebo (15 patients). Due to evident clinical efficacy of anti-interferons used by us in the past it was decided that the placebo group would be smaller than the anti-cytokine groups. We had 5 blocks of patients, 4 patients in

each of the anti-cytokine groups and 3 patients in the placebo group.

All preparations were injected intramuscularly once a day for 5 consecutive days. The first dose of each antibody was 3 ml (approximately 150 mg of protein), the following doses 4 ml (200 mg of protein) each. According to our previous studies these doses were the most appropriate for achieving rapid clinical response in RA patients. Patients were clinically assessed daily for 7 days and then weekly up to the 28th day. During that period no additional therapy was permitted.

Clinical and laboratory indices used for the assessment of treatment efficacy included numbers of swollen and tender joints (the maximum number being 66 joints for swelling and 68 joints for tenderness), duration of morning stiffness, grip strength, patient's assessment of pain and fatigue (visual analogue scale (VAS) ranging from 0—best to 10—worst), patient's and physician's global assessment of their health status (1—excellent, 5—very bad), ESR, and CRP. Functional status was assessed by the Health Assessment Questionnaire (HAQ). All patients were required to have aminotransferases and creatinine within normal limits, hemoglobin level of 90 g/l or greater, platelet count of at least 150,000 and leukocyte count of at least 3200 per cubic millimeter.

Hematology profiles, chemistry profiles and rheumatoid factor (RF) titers were evaluated at baseline, week 1, and week 4.

For ultrasonography Philips sono DIAGNOST 360 with 7.5 MHz linear array was used. Knee joints were chosen for the assessment of the thickness of their synovial membranes by this method because all patients included had clinical signs of bilateral synovitis of these joints. Results obtained were assessed by the observer who was not informed about the specific treatment of patients.

Local ethics committee and Institutional Scientific Board approved the study. All patients gave written informed consent.

Statistical significance was determined using one-sample Student's t-test for the mean difference between values before and after treatment.

3. Results

Baseline demographic and clinical characteristics of our patients were practically identical as shown in **Table 1**. No substantial baseline imbalances were detected. Patients failed previous treatment with approximately 2 DMARDs, mostly with methotrexate and sulfasalazine, each drug having been administered for at least 6 months.

Significantly more anti-cytokine recipients completed full 4 weeks of the trial: 17 of 20 patients on anti-IFN-γ, 16 of 20 on anti-TNF-α, and only 4 of 15 on placebo. Sixteen patients stopped treatment due to lack of efficacy (anti-IFN-γ - 2, anti-TNF-α - 3, placebo - 11). Two patients were withdrawn because of side effects (one in each of anti-cytokine groups). These patients were evaluated on the 7th day but could not be assessed at the end of the trial (**Figure 1**).

In patients receiving anti-cytokines clinical responses were rapid. Considerable clinical improvement (marked reduction in joint pain, tenderness and/or swelling) was noted already after the first injection in 11 patients on anti-IFN-γ, 5 patients on anti-TNF-α, and none on placebo.

The influence of the treatment on the main indices of disease activity is shown in **Table 2** which demonstrates that anti-cytokines were significantly superior to placebo. By the 7th day both anti-IFN-γ and anti-TNF-α produced statistically significant improvement in all 7 clinical measures, whereas administration of placebo led to the improvement in 4 measures that were predominantly subjective. The difference between anti-cytokines and placebo was especially clear at the next stage of the trial. As mentioned above, at the beginning of the 2nd week, 11 of 15 patients on placebo showed evident lack of efficacy or marked deterioration and were transferred to the active conventional therapy (including GCS orally and/or intra-articularly), and withdrawn from the trial. By the 28th day patients in each of anti-cytokine groups demonstrated sustained significant improvement in 7 clinical measures whereas not even one measure improved in the placebo group. Laboratory evidence of improvement was noted only on the 7th day in patients treated with anti-TNF-α (3 indices) and with anti-IFN-γ (one index).

Ultrasound analysis of the thickness of synovial membranes in the knee joints showed that only anti-IFN-γ exerted pronounced anti-inflammatory effect (**Table 3**). Reduction of the thickness of synovial membrane is the most objective sign of the therapeutic (anti-inflammatory) action of anti-IFN-γ. It is noteworthy that this effect of anti-IFN-γ was evident already by the 7th day and was maintained up to at least the 28th day.

Individual results of treatment were assessed in terms of patients who met ACR 20%, 50%, and 70% response

Table 1. Baseline characteristics of patients (where appropriate, values given as means (M ± σ).

Characteristics	Anti-IFNγ	Anti-TNFα	Placebo
No. of patients	20	20	15
Gender, M/F	2/18	5/15	2/13
Age, years	49.30 ± 11.45	50.85 ± 11.39	56.93 ± 9.30
Disease duration, years	9.62 ± 7.49	14.3 ± 8.77	8.13 ± 8.76
Rheumatoid factor +	17	15	13
Pain, VAS, cm	6.15 ± 1.64	6.22 ± 1.47	6.89 ± 1.54
Morning stiffness, min.	129.25 ± 111.05	101.00 ± 105.11	115.33 ± 107.42
Health physician status (1 - 5) patient	3.55 ± 0.51	3.45 ± 0.51	3.46 ± 0.51
	3.70 ± 0.57	3.5 ± 0.51	3.80 ± 0.67
No. of swollen joints	10.60 ± 5.49	10.0 ± 5.31	9.06 ± 2.98
No. of tender joints	21.30 ± 8.35	20.20 ± 7.97	22.73 ± 5.52
Grip strength, right KPa left	31.55 ± 20.71	37.70 ± 22.87	26.13 ± 11.519
	27.45 ± 16.70	33.90 ± 29.53	19.06 ± 6.46
Fatigue, VAS, cm	6.35 ± 1.81	6.87 ± 1.83	6.97 ± 2.1
Hemoglobin, g/L	113.44 ± 18.27	117.36 ± 18.92	113.5 ± 16.51
ESR, mm/hour	35.83 ± 10.55	34.15 ± 10.92	43.00 ± 12.94
CRP, mg/dL	2.3 ± 1.35	2.37 ± 2.54	2.5 ± 3.39
Patients on stable dose of prednisolone	5	6	4
Number of previous DMARDs	1.9	2.1	1.8

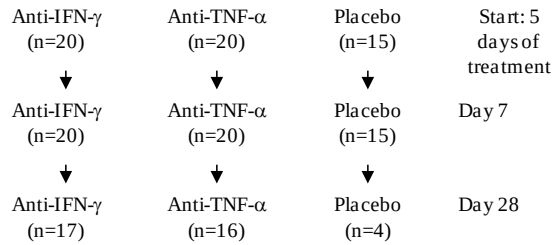

Figure 1. Profile of the study. Note: Drop-outs—Two patients were withdrawn because of side effects (one in each anti-cytokine group). Sixteen patients stopped treatment due to lack of efficacy (anti-IFN-γ - 2, anti-TNF-α - 3, placebo - 11).

criteria (**Table 4**). These data confirm pronounced therapeutic effect of both anti-cytokines. It is especially evident in comparison with the placebo group in which only 2 patients had minimal improvement on the 7th day and none on the 28th. There was a notable difference in response between anti-IFN-γ and anti-TNF-α groups. On the 7th day positive results were noted more often in the anti-TNF-α group (18 of 20 patients, $p < 0.05$) than in the anti-IFN-γ group (14 of 20). On the 28th day the total numbers of ACR responders were similar in the anti-cytokine groups, but the ACR maximum response rate was significantly greater in patients treated with anti-IFN-γ. No patient in the anti-TNF-α group maintained the 70% improvement achieved previously, whereas the number of ACR 70% responders in the anti-IFN-γ group doubled by this time in comparison with results on the 7th day (6 of 17 patients who completed the trial).

Table 2. Influence of anti-cytokine therapy on main clinical and laboratory indices in patients with rheumatoid arthritis (mean positive change from baseline).

Indices		Anti-IFN-γ		Anti-TNF-α		Placebo	
		Day 7	day 28	day 7	day 28	day 7	day 28
Pain, VAS, cm		2.2*	3.4*	3.7*	3.3*	1.2*	0.65
Morning Stiffness, min		90*	124*	80.5*	80*	57*	65
Fatigue, VAS,cm		3.2*	4.8*	4.4*	4*	1.9*	1.2
Swollen joints		4.5*	5.8*	4.6*	4.1*	0.7	0.2
Tender joints		8.5*	10.4*	10.6*	10.2*	4.5*	1.7
Grip strength, kPa	right	7.5*	8.9*	12.4*	15*	3	8.1
	left	8.1*	10.1*	10.9*	13.4*	2.6	6.2
CRP, mg%		0.25	0.3	1.3*	0.5	0.5	0.7
ESR, mm/h		2.4	1.1	4*	2.9	1.7	0.3
HAQ		0.75*	1.19*	0.61*	0.52*	0.04	0.02

*$p < 0.05$.

Table 3. Influence of anti-cytokines on the thickness of the knee synovial membrane ($M \pm \sigma$, mm).

	Right			Left		
	Baseline	Day 7	Day 28	Baseline	Day 7	Day 28
Anti-IFN-γ	3.69 ± 0.9	3.33 ± 0.6 p < 0.05	3.0 ± 0.62 p < 0.02	3.5 ± 0.55	2.94 ± 1.1 p < 0.05	2.73 ± 1.1 p < 0.02
Anti-TNF-α	3.4 ± 0.15	3.25 ± 0.3 p > 0.5	3.36 ± 0.3 p > 0.5	3.27 ± 0.3	3.17 ± 0.4 p > 0.2	2.96 ± 1.1 p > 0.1
Placebo	3.57 ± 0.4	3.43 ± 0.7 p > 0.8	3.3 ± 0.53 p > 0.7	3.3 ± 0.34	3.22 ± 0.4 p > 0.8	3.32 ± 1.3 p > 0.9

Table 4. Assessment of the treatment results according to ACR response criteria.

ACR response	Day 7			Day 28		
	Anti-IFNγ	Anti-TNFα	Placebo	anti-IFNγ	anti-TNFα	Placebo
20%	8	7	2	3	6	0
50%	3	8	0	5	5	0
70%	3	3	0	6	0	0
Unchanged	6	2	13	3	5	4
Withdrawn	0	0	0	3	4	11

Clinical remissions according to ACR criteria developed in 10 patients: 5 on anti-TNF-α (duration of remission from 4 to 24 months) and 5 on anti-IFN-γ (duration from 4 to 36 months).

The most frequent side effect of anti-cytokine treatment was slight local dermatitis (in all probability allergic) at the sites of injections on the 8^{th} - 11^{th} days (anti-IFN-γ - 13 patients, anti-TNFα - 9) (**Table 5**). It disappeared within 2 - 3 days spontaneously or after administration of anti-histamine drugs. Lupus-like syndrome, angioedema, laryngitis, and stomatitis occurred only in anti-TNF-α recipients between the 7^{th} and the 28^{th} days (in one patient each). Lupus-like syndrome has developed in a 51 year old woman with a typical RA. On the 6-th day after the beginning of treatment arthralgias increased and erythematous skin rash appeared on legs, and temperature increased to 37.4˚C. On the 10^{th} day fever increased to 39.4˚C, skin rash and severe joint pain persisted, anti-dsDNA was 1:160 sp (N: 0), and ANA 39 Units (N: up to 20). Both tests have been negative prior to treatment. On the 12^{th} day 250 mg of methylprednisolone was administered intravenously with subsequent daily dose of methylprednisolone 16 mg orally. By the 19^{th} day joint pain diminished considerably, skin rash disappeared, ANA and anti-dsDNA became negative.

Table 5. Side effects of the anti-cytokine treatment.

	Anti-IFNγ	Anti-TNFα	Placebo
Dermatitis	13	9	0
Fever	1	3	0
Respiratory infections	3	3	0
Herpes simplex	1	2	0
Angioedema	0	1	0
Lupus-like syndrome	0	1	0
Stomatitis	0	1	0
Laryngitis	0	1	0
Total	18	21	0

No adverse reactions were registered in the placebo group. Hematology and biochemistry profiles and urinalyses did not show any pathological changes.

4. Discussion

In previous trials it was established that anti-IFN-γ was a well-tolerated and effective preparation in reducing disease activity in patients with severe RA who failed to respond to any DMARDs [3] [4]. This double-blind study confirms the beneficial effect of anti-IFN-γ in treating serious RA. The degree of improvement in patients treated with anti-IFN-γ was comparable and in some aspects superior to that in patients who received anti-TNF-α.

These results and those of previous trials of antibodies to IFN-γ suggest that IFN-γ plays an important role in the pathogenesis of RA and neutralization or inhibition of this cytokine can be considered a promising approach to the therapy of RA, especially its treatment-resistant forms. Future studies should determine whether repeated or prolonged courses of antibodies to IFN-γ (especially monoclonal humanized or fully human antibodies) can lead to a more pronounced and stable clinical improvement and whether the combination of anti-IFN-γ with conventional DMARDs (especially with methotrexate) can have substantial advantages over monotherapy.

It is noteworthy that our data confirm once more the groundlessness of attempts to treat RA with IFN-γ [14] [15]. Failure of this approach has also been clearly shown in the special double-blind study [16].

This study confirms our general hypothesis that the development of Th1 autoimmune diseases, particularly RA, may be connected with cytokine disturbances and that neutralization of these cytokines can be beneficial [1] [13]. Antibodies to IFN-γ and TNF-α have approximately the same clinical effect, though antibodies to TNF-α often cause complications.

We think that the main pathological role may be played by hyper-produced IFN-γ which induces TNF-α. The development of organ-specific autoimmune diseases may be dependent on the cells that hyper-produce IFN-γ and TNF-α in the particular organ. In RA, IFN-γ or IFN-γ-producing cells have been found in the synovial fluid [17], in psoriasis and alopecia areata—in the skin lesions [18] [19], and in other Th1 autoimmune conditions—at the sites of inflammation. Besides RA, anti-IFN-γ has shown good therapeutic effects in such Th 1 autoimmune diseases as multiple sclerosis [20], type I diabetes [21], autoimmune skin diseases including psoriasis, vitiligo, alopecia areata, pemphigus, and epidermolysis bullosa [22], and in corneal transplant rejection [23]. Anti-IFN-γ could be a universal treatment for different Th1 autoimmune diseases. It is important to remember that some preparations of TNF-α blockers may cause serious complications such as noted by a Swiss pharmaceutical company Serono which in 2005 suspended all work on their TNF inhibitor Onercept [24]. We indicated earlier that in our trial one patient with rheumatoid arthritis developed lupus-like syndrome after treatment with antibodies to TNF-α. Other complications of TNF-α blockers are described in the article of N. Scheinfeld *et al*. [25].

It should be noted that, unfortunately, not enough attention is being paid to such a multifunctional cytokine as IFN-γ. We hope that our article can fill the gap in the assessment of this cytokine. Its neutralization has definite perspectives in the therapy of autoimmune diseases.

Every patient with autoimmune disease has a right to use the best achievements of science (antibodies to IFN gamma) for the treatment of his/her condition.

As far as we know Novimmune (Switzerland) is actively working on antibodies to IFN-γ.

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