Biological Agents for Rheumatoid Arthritis: the First Experience in Evaluating Clinical-Laboratory and Cytogenetic Parameters

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The authors have evaluated the efficacy and safety of a loading dose regimen of three intravenous infusions of the biological agent anti-tumour necrosis factor alfa antibody (infliximab) combined with other conventional agents for treatment of severe rheumatoid arthritis. Seven patients with treatment-resistant, long-standing rheumatoid arthritis were included in the study. Standard clinical assessments (patient visual analogue scale, tender joint score, swollen joint score, duration of morning stiffness, erythrocyte sedimentation rate, C-reactive protein) were performed before and after each infusion. A significant decrease in the majority of measured clinical variables was seen after the first infusion. The treatment was well tolerated in all patients, no significant adverse events were seen. Cytogenetical analysis in somatic cells of the patients failed to detect any serious genotoxic influence of the therapy, meanwhile the cytotoxic action was documented as a decrease in the mitotic activity of cell cultures. In patients with a severe rheumatoid arthritis infliximab induced a fast and significant improvement in the clinical and laboratory disease activity parameters, without any considerable cytogenetical damage or major adverse events.

Key words: rheumatoid arthritis, cytokines, tumour necrosis factor, monoclonal antibody, infliximab

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease effecting the majority of joints and other body systems. The disease is characterized mostly by a progressive destruction of synovial joints. The pathogenesis of RA is still not fully understood. Within synovial tissues, soluble mediators secreted by activated cells trigger inflammatory leukocyte adhesion, infiltration, and synovial fibroblast-like cell activation (1). Such an interaction results in synovial lining layer hyperplasia, pannus tissue formation, and destruction of bone and articular cartilage. Joint damage in RA is mediated by macrophage-derived pro-inflammatory cytokines, particularly the tumour necrosis factor alfa (TNFα) and interleukin (IL)-1, which induce matrix metalloproteinase, nitric oxide synthase production in synovial fibroblasts and articular chondrocytes (2). These enzymes then attack collagen and proteoglycan, leading to destruction of cartilage, nearby bone, and periarticular tissues (3).

Historically, the management of RA has been based on treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) administered to patients in the later phases of the disease when the aggressive nature of the disease has been demonstrated by development of bone damage. The NSAIDs exert a rapid suppressive effect through the blockade of cyclooxygenase and inhibition of prostaglandin, thereby reducing pain, stiffness and inflammation (4). These drugs, however, do not influence cytokines. By contrast, the DMARDs act by a variety of means, the common mechanism being inhibition of pro-inflammatory cytokines. Direct neutralization of cytokines by administering antibodies against them is one of the newest approaches to the treatment of RA. Infliximab – a chimeric monoclonal antibody to TNFα – has been recently introduced for the treatment of active RA. It binds to soluble and memb-

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rane-bound TNFα with high affinity, avidity and specificity. Infliximab directly blocks the activities of cytokine and also induces lysis of TNFα-producing cells, thereby causing substantial elimination of the main source of pro-inflammatory molecules. Multiple clinical trials using anti-TNFα have achieved excellent results in many patients with RA. The treatment produced a rapid and profound benefit for all clinical response variables measured (5–10). Nevertheless, all authors conclude that possible side effects of infliximab still need further investigation. There are no data in the literature on changes of the cytogenetic parameters in RA patients treated with infliximab. Oxidative stress induced by chronic inflammation and therapy with cytostatic drugs favours an increased risk of genomic alterations in rheumatic diseases. Increased rate of cytogenetic damage was detected in therapy-related myelodisplastic syndromes associated to rheumatic disease (11). Mutations induced by oxidative stress in rheumatoid arthritis were found in regulatory genes responsible for the genomic integrity of cell (12, 13) and are linked to the chronisation of the disease (14).

The aim of our study was to evaluate the efficacy and safety of intravenous infusions of the TNFα antibody infliximab combined with other conventional agents for the treatment of severe rheumatoid arthritis. Methods of clinical-laboratory analysis were employed to evaluate the effectiveness and safety of the therapy, while cytogenetical analysis of somatic cells from patients gave information about the cytotoxicity and genotoxicity of exposure.

MATERIALS AND METHODS

Patients and treatment

The study design included three infusions of infliximab at weeks 0, 2 and 6 to patients with active RA. Seven patients who met the acute RA criteria and who did not respond to methotrexate (MTX) or azathioprine (AZA) therapy were treated in the Vilnius University Red Cross Hospital. Cytogenetical analysis was done in Laboratory of Ecological Genetics, Vilnius University. Before infliximab therapy all patients gave their written consent and answered a questionnaire concerning lifestyle factors, work conditions and preceding therapies, as such factors may have an impact on the genetic parameters of somatic cells.

The monoclonal anti-TNFα antibody infliximab (Remicade™, Centocor), was infused intravenously at a dose of 3 mg/kg at the initiation of treatment (week 0) and then after 2 and 6 weeks. Four patients received 3 infusions, while three received 1 or 2 doses of infliximab. During the infusion and for one hour afterwards, the patients were monitored for adverse effects, and vital parameters (blood pressure, pulse, temperature) were measured. Patients were allowed to continue NSAIDS, corticosteroids (≤ 10 mg prednisolone/day) and DMARDs (MTX 7.5–10 mg/week or AZA 100 mg/day). Clinical parameters were evaluated at the day of injection and 3 days after each of infliximab injection. The following response variables were evaluated: patients' assessment of pain (10 cm VAS), duration of morning stiffness, tender joint count (TJC), and swollen joint count (SJC). At each visit patients were evaluated for side effects and laboratory tests were performed. Laboratory analysis consisted of the erythrocyte sedimentation rate (ESR), full blood count with white blood cells differentiation and biochemical analysis, including serum concentration of C-reactive protein (CRP), electrolytes, urea, creatinine, total protein with fractions, liver enzymes, serum antinuclear antibodies and antibodies against double-stranded DNA (dsDNA). Expression of rheumatoid factor (RF) was evaluated during the course of therapy. RF status was considered positive if the Rose–Waaler test was positive (> 40 IU/ml).

Cytogenetical analysis

The genotoxicity and cytotoxicity of the therapy was evaluated by means of cytogenetics. Peripheral blood lymphocytes for cytogenetic analysis were collected before and after each injection of infliximab. For the analysis of genotoxicity of the therapy, two criteria were employed: number of sister chromatid exchanges (SCEs) in peripheral blood lymphocytes and cell replication index (RI). The SCE rate in the cell corresponds to the number of DNA breaks and reunions in sister chromatids of chromosome indicating primary damage of DNA. RI shows the intensity of DNA replication after polyclonal stimulation and may be decreased by a cytostatic or genotoxic compound. As the marker of cytotoxicity, the capability of cells to enter G1 and M phase of cell cycle was measured and expressed as blast-transformation (BT) and mitotic activity (MA). Analysis was done on peripheral blood lymphocytes grown in cell culture for 72 h and specially prepared for metaphase analysis by optical microscopy. In brief, cells were grown in RPMI 1640 containing 12% heat-inactivated fetal bovine serum, 50 μg/ml gentamycin, 2 mM L-glutamine. All reagents were purchased from Sigma (St. Louis, MO, USA). Polyclonal mitogen phytohemagglutinin (PHA, 7.8 μg/ml) was used for cell activation. 10 μg/ml of 5-bromo-2'-deoxyuridine was added at initiation of cultures to obtain differential staining of sister chromatids in a chromosome. To increase the number of mitoses, colchicine (0.5 μg/ml) was

added into the cell cultures for the last 3 h. Cells were harvested by conventional methods – hypotonised in 0.075 M KCl solution and then fixed 3 times in 3:1 ethanol : acetic acid. Air-dried slides were differentially stained by fluorescence plus Giemsa technique. Fifty second division metaphase cells were analyzed for SCE rate where possible. Approximately 200 metaphases of different divisions were scored to evaluate RI. The number of blasts and metaphases among 1000 of cells were counted to calculate BT and MA, respectively.

RESULTS

Seven patients with treatment-resistant, long-standing RA fulfilling entry criteria were enrolled in the study and treated with infliximab. All patients were female with a mean age of 54 years (range, from 44 to 62) and median disease duration of 5 years (range, from 2 to 9 years). Baseline disease status was similar and indicated a relatively severe disease. Table 1 shows main characteristics of all the patients. All patients, with exception of two of them received MTX supplementary to infliximab at a dose 7.5–10 mg/week. For two patients infliximab was combined with AZA (100 mg/day), because MTX had induced pulmonitis in the past. Table 2 shows the dynamics of the clinical-laboratory parameters before and after each infliximab dose. Morning stiffness considerably decreased after the first infliximab dose, and was close to zero by the end of the sixth week of therapy. During the course patients' estimation of pain decreased from 7 to 3 on a 10 cm scale. A significant reduction of tender and swollen joint count was achieved after each dose of infliximab. A paired comparison of disease variables before and after injections of infliximab (Student's t test) revealed a statistically significant decrease of SJC ($P = 0.0022$), as well as of TJC ($P = 0.0024$). After three injections of the drug SJC decreased to zero level, TJC was 6 times lower as compared to baseline. Parameters of acute inflammation (ESR, CRP, alfa2 and gamma proteins) also improved, but not in all cases. The most evident, statistically significant ($P = 0.0484$, Student's t test) effect of the therapy was seen on the serum level of CRP.

During the course of therapy urea, creatinine, and liver enzymes remained normal. No patients were withdrawn from the study due to adverse events. No adverse effects related to infusion were noted, either. Vital parameters remained within the normal range during and one hour after infusion. In two patients a slight respiratory infection was noticed after the first injection of infliximab. In one patient exacerbation of chronic cytomegalovirus infection was noted. Anti-dsDNA did appear in some patients after the third dose of infliximab. No significant changes in the amount of RF were detected during the course of therapy (Table 2).

Cytogenetic damage was studied in peripheral blood lymphocytes from four patients before and after three doses of infliximab. All patients were non-smoking women without any deleterious exposure to occupational or life-style factors before the study. The SCEs level at the baseline ranged from 7.56 to 8.64 SCE per cell (Table 3). A paired comparison of values (Student's t test) before and after infliximab injection revealed a slight fluctuation of SCE/cell in the course of therapy. A statistically significant ($P < 0.05$) increase as well as decrease in the number of SCEs were detected in a few cases. However, by the end of therapy the median number of SCE was comparable to that established at the beginning of the study (7.455 SCE/cell compared to 7.895 SCE/cell). The same fluctuation in cell replication rates was also detected. Paired comparison revealed a statistically significant ($P < 0.05$) increase as well as decrease of RI values during the course of therapy (Table 3). The main values of RI at the beginning of the study (RI = 2.376) and after the last injection (RI = 2.390) were similar.

The capability of lymphocytes to grow in cell culture after stimulation with PHA was evaluated during

Table 1. **Main characteristics of the patients**

Patient	Gender	Age	Duration of disease (years)	Treatment with infliximab (injections)	Treatment with MTX (mg/week)	Treatment with AZA (mg/day)
1	female	62	2	2	–	100
2	female	56	9	2	10	–
3	female	60	7	3	10	–
4	female	44	5	3	7.5	–
5	female	56	7	3	10	–
6	female	45	2	3	7.5	–
7	female	55	4	1	–	100

Table 2. **Clinical response before and after first, second and third injection (3 mg/kg) of infliximab**

Patient	Injection	SJC	TJC	Morning stiffness (min)	VAS	ESR (mm/h)	CRP (mg/l)	Anti ds DNA	Alfa2 globulin	Gamma globulin	RF
1	I[a]	16	40	360	6	29	8	n.d.	8.2	9.5	40
	I[b]	3	5	0	2	26	5	n.d.	9.0	10.0	167
	II[a]	5	8	60	3	44	13	n.d.	4.4	25.0	40
	II[b]	0	4	0	2	33	5	n.d.	9.5	24.1	137
2	I[a]	20	45	90	7	31	13	n.d.	7.4	19.8	40
	I[b]	3	12	0	1	25	9	n.d.	7.2	19.0	40
	II[a]	8	21	0	2	18	10	n.d.	8.4	16.8	61
	II[b]	0	5	0	1	17	7	n.d.	8.0	17.4	40
3	I[a]	14	39	240	7	44	103	–	12.8	16.6	74
	I[b]	6	11	30	4	49	46	–	14.2	17.7	84
	II[a]	5	10	0	3	49	99	–	14.0	18.2	144
	II[b]	1	6	0	3	50	31	–	12.3	19.4	118
	III[a]	0	2	0	5	32	16	1:4	9.1	16.0	81
	III[b]	0	2	0	4	34	9	1:4	8.2	17.2	74
4	I[a]	31	56	90	8	67	184	–	11.9	22.1	500
	I[b]	14	48	0	3	51	<6	–	10.3	20.2	500
	II[a]	5	21	0	5	75	295	–	10.5	21.0	332
	II[b]	1	4	0	3	61	8	–	11.5	20.2	315
	III[a]	9	24	0	4	62	372	1:2	10.8	22.0	342
	III[b]	1	7	0	3	62	167	1:4	9.2	21.3	385
5	I[a]	27	33	180	5	28	8	–	11.2	17.0	40
	I[b]	4	11	0	3	24	<6	–	6.6	15.3	49
	II[a]	1	9	0	3	5	<6	–	8.4	16.7	41
	II[b]	0	4	0	3	2	<6	–	7.2	15.9	40
	III[a]	5	13	0	3	5	<6	–	8.8	16.3	40
	III[b]	1	13	0	2	7	<6	1:4	9.8	12.7	40
6	I[a]	15	39	90	7	70	46	–	11.4	20.6	483
	I[b]	4	4	0	2	45	16	–	10.5	28.4	461
	II[a]	2	6	0	3	23	8	–	11.1	20.1	470
	II[b]	0	3	0	3	23	6	–	9.2	19.2	500
	III[a]	6	27	30	5	88	126	–	13.6	21.8	313
	III[b]	0	4	0	2	85	80	1:2	12.8	22.5	346
7	I[a]	19	52	360	8	98	105	–	12.7	28.3	500
	I[b]	12	25	n.d.	4	56	15	–	12.2	27.7	500

[a] before injection of infliximab, [b] after injection of infliximab.
n.d. – not done.

the course of therapy (criteria MA and BT) in order to detect the cytotoxicity of exposure. Blast-transformation analysis revealed the same tendency as in the case of SCE and RI analysis. However, a gradual decrease in cell mitotic activity was established during the study. A paired comparison with the nonparametric Wilcoxon test revealed statistically significant ($P = 0.0322$) differences between MA values before and after drug injections. By the end of the study the mean MA of cell cultures was rather low and equal to 1.01%. Interestingly, the MA of cell cultures grown at baseline was also relatively low (about 3%). This cytotoxic effect may be partially explained by a previous exposure of the patients to cytotoxic DMARDs such as MTX. However, due to the small scope of the study, further investigations are needed to collect reliable data on the cytotoxicity of combined therapy with infliximab plus MTX.

Table 3. **Dynamics of sister chromatid exchanges (SCE), replication index (RI), mitotic activity (MA) and blast transformation (BT) during therapy with infliximab (3 × 3 mg/kg)**

Patient	Injection	SCE/cell ± SEM	RI ± SEM	BT ± SEM	MA ± SEM
3	I[a]	7.70 ± 0.43	2.166 ± 0.049	31.27 ± 1.42	1.88 ± 0.42
	I[b]	8.86 ± 0.47	2.284 ± 0.053	37.79 ± 1.48 [c]	1.87 ± 0.41
	II[a]	7.40 ± 0.42	2.391 ± 0.050	32.79 ± 1.46	2.41 ± 0.48
	III[a]	8.48 ± 0.51	2.259 ± 0.051	42.46 ± 1.56	1.98 ± 0.44
	III[b]	7.06 ± 0.49 [d]	2.152 ± 0.053	40.66 ± 1.53	1.26 ± 0.35
4	I[a]	7.56 ± 0.40	2.639 ± 0.039	33.76 ± 1.48	4.60 ± 0.66
	I[b]	6.94 ± 0.53	1.537 ± 0.049 [d]	20.63 ± 1.27 [d]	0.89 ± 0.30 [d]
	II[a]	8.08 ± 0.50	2.555 ± 0.044	43.20 ± 1.57	2.80 ± 0.52
	II[b]	7.94 ± 0.51	1.850 ± 0.051 [d]	38.04 ± 1.47 [d]	1.02 ± 0.30 [d]
	III[a]	7.30 ± 0.53	2.429 ± 0.043	30.00 ± 1.44	0.69 ± 0.26
	III[b]	7.64 ± 0.43	2.663 ± 0.042 [c]	21.97 ± 1.27 [d]	1.33 ± 0.35
5	I[a]	7.68 ± 0.40	2.176 ± 0.053	36.13 ± 1.50	2.93 ± 0.53
	I[b]	7.00 ± 0.45	2.119 ± 0.053	31.61 ± 1.47 [d]	1.79 ± 0.42
	II[a]	7.38 ± 0.40	2.188 ± 0.053	36.42 ± 1.51	2.36 ± 0.48
	II[b]	6.34 ± 0.45	2.083 ± 0.049	39.85 ± 1.51	1.04 ± 0.31 [d]
	III[a]	5.22 ± 0.35	1.986 ± 0.055	21.85 ± 1.29	1.07 ± 0.32
	III[b]	7.60 ± 0.47 [c]	2.215 ± 0.052[c]	38.05 ± 1.51 [c]	0.67 ± 0.25
6	I[a]	8.64 ± 0.43	2.522 ± 0.049	32.74 ± 1.48	3.77 ± 0.60
	I[b]	10.66 ± 0.54 [c]	2.524 ± 0.042	43.92 ± 1.48 [c]	2.84 ± 0.49
	II[a]	9.50 ± 0.42	2.272 ± 0.049	40.08 ± 1.53	1.27 ± 0.35
	II[b]	10.06 ± 0.49	2.380 ± 0.049	34.23 ± 1.42 [d]	1.80 ± 0.40
	III[a]	9.92 ± 0.67	2.472 ± 0.049	27.00 ± 1.40	1.00 ± 0.84
	III[b]	7.52 ± 0.48 [d]	2.531 ± 0.045	36.78 ± 1.41 [c]	0.77 ± 0.84

[a] before injection of infliximab, [b] after injection of infliximab.
[c] statistically significantly ($P < 0.05$) more, [d] less, as compared to paired value before infliximab injection, Student's t test.

DISCUSSION

An excellent effect was achieved with anti-TNFα antibody (infliximab) in RA patients resistant to conventional treatment. This was the first trial of infliximab in Lithuania, directed toward suppression of high activity of RA. In our study infliximab decreased pain (measured by VAS), reduced morning stiffness, TJC, SJC, serum inflammation markers (ESR, CRP and alpha-2 globulins). Most of the measured variables improved significantly after the first infusion, and the favorable effect persisted throughout the study (3 doses of infliximab administered). Up to now, two open-label and four placebo-controlled, randomized, double-blinded trials (published) of infliximab have been conducted in approximately 650 RA patients worldwide (15). A significant and fast favorable clinical effect of infliximab was documented by these studies (reviewed in 16–17). These studies showed that a combined treatment with infliximab and MTX was superior to monotherapy with infliximab (8). MTX increased the duration of response and reduced the development of anti-infliximab antibodies. Besides, recent radiographic studies of infliximab plus MTX therapy revealed the possibility to halt progression of joint damage in RA patients (10). In our pilot study, infliximab was combined with MTX (7.5–10 mg/week) or AZA (100 mg/day) according to international recommendations (17–18). The infusion of infliximab was well-tolerated and no major adverse effects were reported in our study. Serum electrolytes, urea, creatinin, liver enzymes also remained within the normal range. Experience from the other trials shows that acute infusion reactions (headache, fever, chills, urticaria, chest pain) may develop in patients receiving infliximab (19). Antinuclear and anti-dsDNA antibodies were reported in 10% of patients, drug-induced lupus was seen in less than 1% of them and resolved upon discontinuation of the drug (19). In our case, the appearance of anti-dsDNA was registered only after the third injection of infliximab.

In our study, two cases of slight upper respiratory tract infections and exacerbation of chronic cytomegalovirus infection were noticed. Upper respiratory and urinary tract infections were most frequently reported by other authors (17). Seven cases of malignancy (5 new and 2 recurrent) were reported to occur among 771 patients treated with infliximab (17). It composed 0.8% of the study group and did not exceed the rates detected in untreated populations. However, in patients with serious infections or malignancy the use of anti-TNF therapies is not advised (18).

In order to increase the safety control of our study, conventional clinical-laboratory testing of patients was supplemented with cytogenetical analysis. The analysis revealed normal rates of SCE (median 7.895 SCE/cell) at baseline and an increase or decrease (fluctuation) of SCE/cell value after injections of infliximab. A statistically significant ($P = 0.0322$, Wilcoxon test) decrease in MA of cells after injections of infliximab detected in our study revealed a possible cytotoxicity of the treatment. As far as we know, no studies on the genotoxicity of infliximab in patients with RA have been conducted. The genotoxicity of TNFα (20) and of the induced nitric oxide (21) was demonstrated in cell cultures, meanwhile the blockade of TNFα with infliximab should suppress both these factors, thereby reducing the genotoxic and cytotoxic effects of TNFα. Therefore, the cytotoxic effect observed in our study can be explained as a negative effect of MTX. The genotoxicity and cytotoxicity of MTX were shown in different studies (22). However, only this effect in RA patients has been studied (23). The authors succeeded to reduce the level of MTX-induced genetic damage (chromosome aberrations and micronucleus) by administering folic acid to the patients.

Our small study revealed the excellent clinical efficacy and acceptable safety profile of therapy with infliximab in RA. All patients are still in follow-up to report the longer-term efficacy of this induction.

CONCLUSIONS

1. The monoclonal antibody to TNFα (infliximab) is an effective drug for the treatment of severe, treatment-resistant RA. In combination with MTX or AZA it induced a fast and significant decrease in disease variables measured during our study.

2. Infusion of infliximab is well tolerated, no major adverse effects were reported in our study. A slight increase in the number of upper respiratory tract infections was detected.

3. Evaluation of treatment safety gave favorable results. Laboratory tests failed to detect any signs of treatment toxicity. However, analysis for cytotoxicity revealed a significant decrease in the mitotic activity of peripheral blood lymphocytes in some patients, probably caused by MTX.

4. Treatment to infliximab plus MTX or AZA is not genotoxic. No stable and permanent increase in the number of genetic damage was detected in somatic cells of the patients during our study.

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BIOLOGINĖS MEDŽIAGOS REUMATOIDINIO ARTRITO TERAPIJOJE: INFLIKSIMABO POVEIKIS KLINIKINIAMS, LABORATORINIAMS IR CITOGENETINIAMS RODIKLIAMS (PIRMOJI PATIRTIS LIETUVOJE)

S a n t r a u k a

Infliksimabas – tai monokloninis antikūnas prieš navikų nekrozės α faktorių. Vaistas neseniai aprobuotas reumatoidiniam artritui ir Krono ligai gydyti. Lietuvoje tik pradedama gydyti šiuo preparatu. Studijos metu buvo vertinamas terapijos infliksimabu efektyvumas ir saugumas, taip pat galimas poveikis citogenetiniams rodikliams. Septyniems RA pacientams, kuriems nepadėjo visos išbandytos bazinės terapijos priemonės, buvo skiriamos 3 infliksmabo infuzijos po 3 mg/kg (0, 2 ir 6 savaitę). Prieš kiekvieną infuziją ir po jos buvo vertinami klinikiniai ligos aktyvumo rodikliai (pacientų skausmo įvertinimas, rytinis sustingimas, sutinusių ir skausmingų sąnarių skaičius), atliekami laboratoriniai tyrimai (ENG, CRB, RF, alfa2 ir gamma globulinai, anti-DNR, kepenų fermentai, kreatininas, urea, elektrolitai) ir citogenetiniai tyrimai (SCM, RI, MA). Didžioji dalis klinikinių ir laboratorinių ligos aktyvumo rodiklių sumažėjo jau po pirmosios vaisto infuzijos. Teigiamas klinikinis efektas išliko per visą tyrimą. Vaistas buvo gerai toleruojamas, nepastebėta jokių ryškesnių pašalinių efektų. Citogenetiniai tyrimai parodė, kad terapija yra pakankamai saugi ir nesukelia ženklesnių genetinių pažeidimų pacientų somatinėse ląstelėse. Tyrimo rezultatai parodė, kad infliksmabas yra veiksmingas ir saugus biologinis preparatas, galintis padėti ligoniams, kuriems jokia iki tol taikyta bazinė terapija nedavė gerų klinikinių rezultatų.