Treatment of Rheumatoid Arthritis with Biologic DMARDs (Rituximab and Etanercept)

Afrim A. Gashi, Sylejman Rexhepi, Idriz Berisha, Avni Kryeziu, Jehona Ismaili, Gezim Krasniqi

Clinic of Rheumatology, University Clinical Centre of Kosova, Prishtina

Corresponding author: Afrim A. Gashi, MD, Clinic of Rheumatology, University Clinical Centre of Kosova, Prishtina

ABSTRACT

Goal: To determine efficacy and safety of treatment with Rituximab and Etanercept plus Methotrexate in patients with active Rheumatoid Arthritis (RA), who had an inadequate response to nonbiologic DMARDs therapies and to explore the pharmacogenetics and pharmacodynamics of Rituximab and Etanercept in our populations. Study was done at Rheumatology Clinic of University Clinical Centre in Prishtina during 2009-2011 years. **Methods:** We evaluated primary efficacy and safety at 24 weeks in patients enrolled in the study of long term efficacy of Rituximab and Etanercept. Patients with active Rheumatoid Arthritis and an inadequate response to 1 or more non biologic DMARDs were randomized to receive intravenous Rituximab (1 course consisting of 2 infusions of 1.000 mg each –one group, and Etanercept 25 mg twice weekly –second group, but both groups with background MTX. The primary efficacy end point was a response on the ACR 20%, improvement criteria at 24 weeks, Secondary end points were responses on the ACR 50 and ACR 70, improvement criteria, the DAS 28, and EULAR response criteria at 24 weeks. **Results:** During our investigations we treated 20 patients, 15 females and 5 males, in the treated group with RTX and 13 patients 8 females and 5 males in the treated group with ETN. Patients of group 1 and group 2 were of ages 37-69 years old and 19-69 years old (average 47-44) Most of the patients belong in 2nd and 3rd functional stage according to Steinbrocker. All ACR response parameters were significantly improved in RTX treated patients who also had clinically meaningful improvement in fatigue, disability and quality of life. Patients showed a trend less progression in radiographic end points. Most adverse events occurred with the first RTX infusion and were mild to moderate severity. **Conclusion** At 24 weeks, a single course of RTX and ETN provided significant and clinically meaningful improvements in disease activity in patients with active, longstanding RA who had an inadequate response to 1 or more nonbiologic DMARDs.

Key words: Rheumatoid Arthritis, ACR, Rituximab, Etanercept.

1. INTRODUCTION

Rheumatoid arthritis is a chronic systemic autoimmune disease characterized by symmetric inflammation of affected joints (1,2). The disease affects 1% of the population (3) and has been a significant cause of disability (4, 5). Over the last 3 decades, there have been significant improvements in patient outcomes associated with the introduction of MTX in the 1980 and the subsequent shift to its earlier and more intensive use. The development of therapies targeting tumor necrosis factor (TNF) and interleukin 1 has resulted in further improvement in outcomes, related to the capacity of these treatment to retard radiographic progression of RA. Even with the advances in disease management, a population of patients with refractory RA exists. In clinical trials that lead to approval of anti TNF therapies, 25-40% of patients failed to achieve a response on the American College of Rheumatology 20% improvement criteria (ACR 20) (6, 7, 8, 9).

Reporting on the Swedish Society of Rheumatology registry of patients with RA treated with Etanercept between 1999-2003 found that 21% of RA patients initiating therapy with Etanercept were no longer receiving this therapy at 24 months (10). A preliminary study from the Stockholm TNF antagonist follow up registry found that

only 44% of patients were still taking their original therapy at 5 years, and 25% were no longer taking any of TNF L antagonist at all (11). While the etiology of RA remains elusive, it is believed that unknown antigenic triggers, initiated within the background of genetic, environmental and hormonal influences, initiate a self perpetuating cascade of autoimmune inflammatory responses within synovial compartment (2,12). Specific B and T lymphocytes, macrophages, monocytes endothelial cells, fibroblasts play putative roles in this process.

Recent research indicates that B cell may act at multiple levels of the inflammatory cascade by disrupting antigen presentation by T cells as well as inducing an increased expression of proinflammatory damage observed in RA (12). Rituximab is a genetically engineered chimeric monoclonal antibody that targets CD20+ B cells.

CD20 is an attractive target for B cell depleting therapy because it is stable and highly expressed on B cells but not on stem cells or plasma cells.

2. MATERIAL AND METHODOLOGY

Eligible patients were hospitalized on Clinic of Rheumatology in University Clinical Centre in Prishtina.

Patients had RA at least 5 years, according to the ACR

Type of treatment	N	%	Average of morning stiffness in minutes			p-value
			Before treatment	After treatment	t-test	
With Etanercept	13	36.1	63.3±13	29.8±10.7	6.9	p<0.00001
With Rituximab	23	63.9	62.3±9.3	43.5±8.6	7.1	p<0.0001
Total:	36	100.0	62.7±11.2	38.6±11.4	9.1	p<0.0001

Table 1. Average of morning stiffness before and after treatment

Figure 1. Percentage of treated patients according to their gender

1987 revised criteria (25), and had active disease, which was defined as >8swollen joints(of 66 joints assessed) and> 8 tender joints (of 68 joint assessed), a C reactive protein (CRP)level >16 mg/l or an ESR >28mm/hour, and radiographic evidence of at least 1 joint with a definite erosion.

3. RESULTS OF INVESTIGATION

Eligible patients had to be taking MTX (10-25 mg week), for at least 12 weeks, with the least 4 weeks at a stable dosage. Patients of I group received intravenous infusions of RTX on days 1 and 15. Patients of 2 group received Etanercept 50 mg divided on two doses (two times a week). Both groups continued to take stable dosages of MTX (10-25 mg) weekly orally and received folate (5 mg/week), intravenous sol. NaCl 0.9%100 ml +Methylprednisolone amp. 100 mg +amp. Synopen 30 min before each infusion and oral Prednisone 60 mg on day 2-7, 30 mg on days 8-14 during 2 weeks.

Primary efficacy and safety were evaluated at 24 weeks, after 24 weeks patients entered a “post treatment period” and were followed up every 2 months for 18 months, for an overall study duration of 24 months.

Patients had longstanding (5 years), and active disease as determined by elevated levels of markers of inflammation, DAS 28, Genant modified Sharp radiographic scores and number of swollen and tender joints. A majority of patients in each group (85%)were RF positive. 89% of patients in both groups had received DMARDS other than MTX (Sulfasalazine 2.0 daily, Hydroxychloroquine 400 mg).

Glucocorticoids most commonly Prednisone and triamcinolone were taken by 61% of the RTX group and 65% of the Etanercept group. Notably at week 24 the swollen and tender joint counts, CRP levels and ERS were significantly decreased in both groups. The CRP level decreased by a mean of 8 mg/l in Rituximab treated patients and 7 mg/l in Etanercept group.

Type of treatment	N	%	Average of morning stiffness in minutes			p-value
			Before treatment	After treatment	t-test	
With Etanercept	13	36.1	63.3±13	29.8±10.7	6.9	p<0.00001
With Rituximab	23	63.9	62.3±9.3	43.5±8.6	7.1	p<0.0001
Total:	36	100.0	62.7±11.2	38.6±11.4	9.1	p<0.0001

Table 2. Gender structure of the patients in 1st and 2nd group (Rituximab and Etanercept)of the patients in 1st and 2nd group (Rituximab and Etanercept)

Type of treatment	N	%	Average of morning stiffness in minutes			p-value
			Before treatment	After treatment	t-test	
With Etanercept	13	36.1	63.3±13	29.8±10.7	6.9	p<0.00001
With Rituximab	23	63.9	62.3±9.3	43.5±8.6	7.1	p<0.0001
Total:	36	100.0	62.7±11.2	38.6±11.4	9.1	p<0.0001

Table 3. Pain modality after treatment

Biologic markers	Number of patients	
	Rituximab (n=20)	Etanercept (n=13)
RF (Waler Rose)	>15iu/ml	>11iu/ml
ERS	>28mm H2O	>30mm H2O
PCR	>17mg/l	>20mg/l

Table 4. Mean value of inflammatory markers before treatment

Sex	N	%	Average age ± SD
Female	22	61.1	52.3 ± 9.9
Male	14	38.9	49.1 ± 13.0
Total:	36	100.0	51.1 ± 11.1

Table 5. Average age of the sample axaminees

Figure 2. Average of stiffness in minutes before and after treatment.

ERS decreased by a mean of 18 mm/h in RTX treated patients, compared with decrease of 17 mm/h in Etanercept treated patients. Changes in radiographic end points at week 24 showed less progression of joint damage (joint narrowing, erosions).

RTX in RA treatment was associated with a mean decrease in RF levels (55%), whereas treatment in Etanercept group with a mean decrease in RF levels (49%).

4. DISCUSSION

Overall 88 % of Rituximab treated patients reported no adverse event during treatment. Aes were mild or moder-

ate (two patients during the first infusion had chest pain, fatigue, cough, headache). On ETN group 1 patient had nausea and injection site reaction which develop in 10% of patients (itching, pain, swelling.) In patients who experienced a severe infusion related reaction the infusion was immediately interrupted. After all symptoms disappeared the infusion was restarted at half the rate that had precipitated the reaction.

There were no reports of tuberculosis or opportunistic infections over the 24 weeks of this evaluation. For patients who experienced an infusion reaction the recommended treatment included acetaminophen /paracetamol plus intramuscular or slow intravenous administration of antihistamine (diphenhydramine HCL) and bronchodilator if indicated.

Etanercept, recombinant p 75 s TNF: Fc fusion protein

Has received approval from the US food and Drug Administration for patients with RA who had failed treatment with at least one other drug. The therapeutic effects mediated by Etanercept are rapid and sustained. Combining Etanercept with MTX was found to be safe and more effective than treatment with MTX alone in the treatment of RA.

Patients received subcutaneous injection of Etanercept 0.25 mg twice weekly for 24 weeks. In our study 13 patients with RA (inadequate response to 1-4 prior DMARDS) were randomized to have at least one of the following: ERS>28mm/h, CRP>16mg/l, morning stiffness at least 45 min. Etanercept produced a significantly greater improvement in all primary and secondary measures of disease activity. The most common Etanercept associated adverse event is injection site reaction, which develop in 37% of patients. This reaction is characterized by development of mild erythema, itching, pain and swelling. The frequency of injection site reaction diminishes with time. In most RA patients these reactions do not necessitate drug discontinuation or require treatment.

5. CONCLUSION

Our results demonstrate that a single course of two 1.000 mg infusions of Rituximab given 2 weeks apart, in combination with glucocorticoids and background MTX, produced significant clinical and functional benefits at 24 weeks in patients with longstanding and active RA who

had an inadequate response to nonbiologic DMARDS.

The therapeutic effects mediated by Etanercept are rapid and sustained. Combining Etanercept with Methotrexate was found to be safe and more effective than treatment with MTX alone in the treatment of RA.

CONFLICT OF INTEREST: NONE DECLARED

REFERENCES

1. Lange. Current diagnosis and treatment on Rheumatology, 2.nd edition, Lange Medical Books. Mc Graw Hill, Medical Publishing Division, New York, Chicago, San Francisco; 2007; 67: 522-532.
2. Hochberg MC, Chane RW, Dwosh I, Lindsay S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. *Arthritis Rheum* 1992; 25: 498-502.
3. Firestein. Kelly textbook of Rheumatology, 8.th edition; WB Saunders Company. 2008; 52: 330.
4. Lange. Basic Radiology. 2.nd edition, Medical Graw Hill; New York, Chicago; San Francisco, 2011; 3: 155-163.
5. Van Riel PLCM. Provisional guidelines for measuring disease activity in clinical trials on RA. *Br.J Rheumatol.* 1992; 31: 793-796.
6. Rexhepi S. *Reumatologjia*. Prishtine, 2006; 7: 208-214.
7. Rheumatoid Arthritis Clinical Trial. Archive group. The effect of age and renal function on the efficacy and toxicity of Methotrexate in Rheumatoid Arthritis. *Arthritis Rheum.* 2005; 52: 2975-2983.
8. Smolen J. et al. A survey of British Rheumatologists DMARDS preferences for rheumatoid arthritis. *Rheumatology.* 2004; 43: 206-210.
9. Hochberg MC, Chane RW, Dwosh I, Lindsay S, Pincus T, Wolfe F. The American College of Rheumatology, .1991 revised criteria for the classification of global functional status in rheumatoid arthritis. *Arthritis rheum.* 1992; 25: 498-502.
10. Kremer J, Alercon M, Light GS, Foot RW Jr. et al. Methotrexate for Rheumatoid Arthritis. *Journal.* 1994; 37: 316-328.
11. Persellin RH. Treatment in Rheumatoid arthritis. Në: Mc Carty DJ (red.) *Arthritis and Allied Conditions*. Philadelphia: Lea and Febiger, 1985; 643-59
12. Smolen J et al. (2005) Superior efficacy of combination therapy in rheumatoid arthritis: fact or fiction? *Arthritis Rheum* 52: 2975-2983.