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Treatment of Rheumatoid Arthritis with Golimumab Against the Disease Modifying Anti-Rheumatic Drugs and Infliximab Resistance

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Abstract

The safety and efficacy of Golimumab 50 mg (GLMB), for the treatment of rheumatoid arthritis (RA), was investigated by selecting the patients with resistance against the Infliximab and disease modified anti-rheumatic drugs (DMARDs). The patients with resistance to the Infliximab and DMARDs about 50 members were selected and divided into 2 groups as group A and group B. The investigational drug GLMB and placebo were administered to the group A and group B respectively. At predetermined intervals, the samples were collected and analyzed for the concentration of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) present in the synovial fluid. After administration of test drug and placebo, the samples were collected at regular intervals of every 4 weeks upto 24 weeks and analyzed. The concentrations of TNF-α and IL-6, before and after administration of test drug, were compared and observed that the GLMB showed better efficacy than that of the placebo. It could be concluded from the results that the safety and efficacy of the investigational product has been achieved.

Key words: Cytokines, Efficacy, Golimumab, Multidrug resistance, Rheumatoid arthritis.

1. Introduction

RA is a chronic autoimmune disease characterized by inflammation of the synovial joints which leads to the progressive destruction of the bone [1]. Human life is not possible when the movement of the joints challenged and the cytokines are responsible for the inflammation in the joints [2]. RA is more widespread disease and its presence caused sharp degrade in the physical and mental health of the people. This disease can affect at any age of the people but peoples with the age of 40 to 70 years are more prone to the

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disease and most commonly, women than men, old age and economically backward families are affected [3]. It is evident that it may reduce the life expectancy by 3-20 years [4], particularly in older women leads to pain, disability and finally mortality may occur [5-6].

TNF-α and IL-6 are the proteins produced by immune cells and these proteins can act on other cells to help, regulate and promote an immune response. IL-6 is also stimulates the production of acute phase reactants and proteins whose concentrations are more in the blood during the inflammatory conditions or tissue injury [7]. DMARDs are the most commonly using drug category for the treatment of RA and Methotrexate is the commonest drug among the DMARDs [8]. But in recent days, DMARDs usage was reduced due to the resistance developed by the patients and those were replaced by newly developed biological agents to treat the RA [9]. These agents have the mechanism to block the pro-inflammatory cytokines such as TNF-α and IL-6 which have the role in pathophysiology, diagnosis and treatment of RA [10].

Some of the well-known biological agents such as Infliximab and Etanercept showed a marked anti-rheumatic activity but their well-known efficacy over the DMARDs still needs to be developed for the treatment of early RA [11]. Hence, in the present study, the step has been taken to predict the efficacy of novel biological agent GLMB in the treatment of RA against the DMARDs and Infliximab resistance. The concentration of TNF-α and IL-6 in the synovial fluid are used to monitor the effect of investigational product.

2. Experimental

2.1. Volunteer's selection and drug administration

Volunteers about 50 members who are not responding or showing resistance to the treatment with Infliximab and other DMARDs were selected. All the patients were satisfied the revised classification criteria described by the American College of Rheumatology, 1987 [11]. Then the volunteers were administered with the drug GLMB 50 mg and placebo by subcutaneous route (front of middle thighs).

2.2. Sample collection and analysis

At each monthly visits (at 4 weeks interval upto 24 weeks), 1-2 ml of synovial fluid was collected into special containers which meant for the collection of synovial fluid. The collected samples were immediately taken to the diagnostic labs (Hyderabad) where the samples were analyzed for the concentration of IL-6 and TNF-α. If any subject shows adverse events, those will not consider for the analysis followed by withdrawn from the study.

2.3. Statistical analysis

The data was expressed in mean ± standard deviation (SD) and standard error (SE). One way and multiple ways ANOVA was applied using GraphPad Prism 6 and significance was set at $p<0.0001$, and $p<0.05$.

3. Results

The current clinical study emphasizes the effect of GLMB in RA patients with Infliximab and DMARDS resistance. Initially, the study population consists of 50 members and divided into two groups with 25 members each. During the study, 3 members showed adverse events, hence those were withdrawn from the further studies. Among the 47 patients studied, 40 and 7 patients were females and males respectively. Whose average age was found to be 64.7 ± 9.93 years and disease duration was 16.9 ± 11.3 years.

Their TNF-α and IL-6 amounts were determined as 18.15 ± 1.79 pg/ml and 23.3 ± 5.7 pg/ml respectively. The group A was administered with the test drug GLMB 50 mg and group B with placebo. The study was continued for 24 weeks and the samples were collected at predetermined intervals of every 4 weeks. The collected samples were subjected to analysis for the estimation of concentration of TNF-α and IL-6 present in the samples. It was observed from the obtained analytical data, as the duration of treatment prolonged i.e. upto 24 weeks with GLMB, the concentration of TNF-α and IL-6 were fallen down than that of the treatment with placebo. It was noted that the treatment with GLMB, at 24th week, the concentrations of TNF-α and IL-6 were found to be 10.60 pg/ml and 12.73 pg/ml respectively while the treatment with placebo, the concentrations were determined as 15.33 pg/ml and 20.02 pg/ml respectively (Table 1-2). The decrease in the concentrations of biomarkers such as TNF-α and IL-6, clearly indicating that the treatment of RA with GLMB is a suitable approach for the patients with DMARDs and infliximab resistance. Efficacy studies such as clinical response, clinical remission and mucosal healing confirmed that the test drug possessing more efficacy than that of the placebo (Table 3).

4. Discussion

The main objective of the present research was aimed to estimate the efficiency of GLMB in the treatment of RA patients with infliximab and DMARDs resistance. The concept of multi drug resistance (MDR) has occupied a little space in the treatment of RA but not much more as like cancer therapy and microbiological studies. A large number of studies have carried out for knowing the role of MDR protein expression in cancer chemotherapy but similar studies have not been performed for RA to determine the therapeutic efficacy of DMARDs. Few studies have attempted to know the role of MDR or patient characteristics in RA. They observed that MDR is not solely responsible for drug resistance in RA but also some other factors such as subject variability are also a cause of RA. Hence, this study confirmed that MDR is not all due to the bankruptcy of drug efficacy [12]. Maillefert studied a role of DMARDs resistance and MDR expression where he observed that the significant increase in the percentage of Pgp+ peripheral blood lymphocytes in RA patients who treated with prednisone compared to the patients treated with DMARDs. He predicted that the steroids decreases the efficacy of some DMARDS by reducing their intracellular accumulation through an enhancement of Pgp expression, it also may be a one more cause of DMARDs resistance in RA [13].

The TNF-α and IL-6 are the important multifunctional cytokines and their concentrations are also decides the severity of the inflammatory diseases. Most of the TNF-α blockers are the biological medications and those are not only used in the treatment of arthritis in joints but also the spinal arthritis associated with RA and related diseases [14-15]. In healthy subjects, IL-6 concentration is absent or may be present in low quantities. An elevated IL-6 levels may mean that the person is suffering with inflammatory events. IL-6 is elevated with a variety of conditions and has been associated in some cases with an increased risk of disease development or worsening prognosis. Hence, the IL-6 concentration is helpful in evaluating the diseases associated with inflammatory conditions and some extent, it is also used in the evaluation of diabetes or cardiovascular diseases [7, 16-17].

Table 1. Amount of IL-6 obtained in the synovial fluid at different intervals.

At week 4			**At week 8**	
Number of subjects	22	25	22	25
Minimum	17.90	18.30	17.00	17.80
Median	20.35	23.20	18.85	22.80
maximum	23.40	27.60	24.30	27.00
Mean	20.55	23.16	19.55	22.67
SD	1.746	2.470	1.963	2.480
SE	0.3723	0.4940	0.4186	0.4959
Lower 95% CI	19.78	22.14	18.67	21.65
Upper 95% CI	21.32	24.18	20.42	23.70
P value	<0.0001	0.0408 (<0.05)	<0.0001	0.0385 (<0.05)
P value summary	***	*	***	*
Significance	Yes	Yes	Yes	Yes
At week 12			**At week 16**	
Number of subjects	22	25	22	25
Minimum	15.60	17.00	14.10	16.50
Median	17.50	22.30	16.00	21.70
maximum	22.80	26.60	20.40	26.00
Mean	18.24	22.20	16.55	21.72
SD	1.955	2.471	1.909	2.493
SE	0.4169	0.4941	0.4071	0.4986
Lower 95% CI	17.37	21.18	15.71	20.69
Upper 95% CI	19.11	23.22	17.40	22.75
P value	P<0.0001	0.0734 (<0.05)	P<0.0001	0.0469 (<0.05)
P value summary	***	ns	***	*
Significance	Yes	No	Yes	Yes
At week 20			**At week 24**	
Number of subjects	22	25	22	25
Minimum	12.10	16.10	10.50	14.80
Median	13.95	20.70	12.15	19.80
maximum	18.20	25.30	16.10	24.60
Mean	14.61	20.83	12.73	20.02
SD	1.985	2.314	1.932	2.423
SE	0.4233	0.4627	0.4118	0.4846
Lower 95% CI	13.73	19.88	11.87	19.02
Upper 95% CI	15.49	21.79	13.58	21.02
P value	P<0.0001	0.0579 (<0.05)	P<0.0001	0.0311 (<0.05)
P value summary	***	ns	***	*
Significance	Yes	No	Yes	Yes

SD-Standard Deviation; SE-Standard Error; CI-Confidential Interval; ns-not significant.

Table 2. Amount of TNF-α obtained in the synovial fluid at different intervals.

At week 4			**At week 8**	
Number of subjects	22	25	22	25
Minimum	13.00	15.40	12.40	14.90
Median	15.80	17.40	14.80	16.90
maximum	17.80	19.20	16.70	18.70
Mean	15.53	17.32	14.55	16.90
SD	1.495	1.007	1.345	1.030
SE	0.3188	0.2014	0.2867	0.2061
Lower 95% CI	14.86	16.90	13.96	16.47
Upper 95% CI	16.19	17.74	15.15	17.33
P value	<0.0001	0.3587 (<0.05)	0.0001	0.4504 (<0.05)
P value summary	***	ns	***	ns
Significance	Yes	No	Yes	No
At week 12			**At week 16**	
Number of subjects	22	25	22	25
Minimum	11.20	14.60	10.60	14.20
Median	13.65	16.50	12.55	16.50
maximum	15.40	18.50	14.60	18.20
Mean	13.50	16.54	12.44	16.21
SD	1.311	1.073	1.272	1.101
SE	0.2796	0.2146	0.2711	0.2202
Lower 95% CI	12.91	16.10	11.88	15.75
Upper 95% CI	14.08	16.99	13.00	16.66
P value	<0.0001	0.5760 (<0.05)	<0.0001	0.3206 (<0.05)
P value summary	***	ns	***	ns
Significance	Yes	No	Yes	No
At week 20			**At week 24**	
Number of subjects	22	25	22	25
Minimum	10.10	13.80	9.40	13.30
Median	11.60	16.00	10.45	15.70
maximum	13.50	17.80	12.80	17.20
Mean	11.62	15.74	10.60	15.33
SD	1.013	1.161	0.9304	1.144
SE	0.2159	0.2322	0.1984	0.2287
Lower 95% CI	11.17	15.26	10.19	14.86
Upper 95% CI	12.07	16.22	11.01	15.80
P value	<0.0001	0.3118 (<0.05)	<0.0001	0.3308 (<0.05)
P value summary	***	ns	***	ns
Significance	Yes	No	Yes	No

SD-Standard Deviation; SE-Standard Error; CI-Confidential Interval; ns-not significant.

Table 3. Efficacy end points.

Efficacy score (sustained end points)	**GLMB**	**Placebo**
Clinical response (%)	23.8	12.2
Clinical remission (%)	8.5	4.1
Mucosal healing (%)	18.5	10.6
P value	<0.05 (**Significant)	ns (not significant)

In the present study, the MDR patients who had stopped 3 or more DMARDs due to the lack of efficacy were selected and Most of the MDR patients were likely to be females. The concentrations of TNF-α and IL-6 in the synovial fluid were used to monitor the effect of the investigational product. Group A and B patients were administered with GLMB and placebo respectively. Samples were collected at the intervals of every 4 weeks upto 24 weeks and the results were depicted in table 1-2. It was observed from the results that the concentrations of TNF-α and IL-6 were decreased with the increase in the duration of the treatment. Significant studies confirmed that the obtained results were significant i.e. $P<0.0001$ in case of TNF-α and $P<0.05$ in case of IL-6. From the questionnaire reports obtained from the patients, the efficacy of the drug has been measured in terms of increase in three criteria such as clinical response, clinical remission and mucosal healing. There was an increase in the clinical response in patients by 11.6% more than that of placebo and also in patients treated with the GLMB, it was observed that the 4.4% and 7.9% more increase in the clinical remission and mucosal healing respectively than that of the placebo (Table 3). This study clearly revealed that the treatment with GLMB is a suitable approach for the patients with DMARDs and infliximab resistance.

5. Conclusion

Patients with active RA showed significant improvement in physical function, general health and fatigue following GLMB 50 mg therapy and general health was maintained throughout the 24 weeks. It worked as an effective biological agent by significantly reducing the inflammation causing cytokines. From the clinical data, it could be concluded that the study objectives such as safety and efficacy of the test product has been achieved. Based on clinical and statistical data obtained from the patients, it has been observed that a dose of 50mg GLMB given subcutaneously was safe and effective to treat the RA. This study is still continuing for the diseases associated with inflammation like ulcerative colitis.

6. Conflict of Interest

The author(s) report(s) no conflict(s) of interest(s). The author along are responsible for content and writing of the paper.

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NA

8. References

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