The Pharma Innovation Journal 2019; 8(4): 94-98

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(4): 94-98

www.thepharmajournal.com
Received: 26-02-2019
Accepted: 28-03-2019

Dr. Sarah Tareq Abdul Azeez
Rheumatology Units, Baghdad Teaching Hospital, Baghdad, Iraq

Correspondence
Dr. Sarah Tareq Abdul Azeez
Rheumatology Units, Baghdad Teaching Hospital, Baghdad, Iraq

Changes in the blood tests in Iraqi patients with active rheumatoid arthritis receiving rituximab

Dr. Sarah Tareq Abdul Azeez

Abstract
Rheumatoid arthritis (RA) is chronic inflammatory systemic disease that affect synovial membrane of peripheral joints leading to loss of daily function because of pain and fatigue. Rituximab is one of biologic agents used for RA. Its a chimeric monoclonal antibody directed against CD20 protein on the B cell surface used for treatment of sever active form of disease. Its control the disease activity with few side effects. The effects of Rituximab on blood values (like ESR, ACPA,RF, Hb, WBC, SGOT, SGPT, S cr, blood urea) were demonstrated in this study on 65 RA patients receiving RTX in the Rheumatology ward in Baghdad Teaching Hospital between June2015 and January 2017. All of them diagnosed according to ACR criteria 2010 and had severely active disease. All patients were received four doses of RTX over 6 months and blood sample were taken at each visit

Results: Data analysis shows significant improvement in the Hb level (P value = 0.005) and significant decreasing in ESR (p value = 0.005) and ACPA (p value = 0.005).There is no significant changes in the other parameters.

Conclusions
1. The use of RTX for 6 ms decreases the disease activity by decreasing ESR and ACPA
2. The use of RTX for 6 ms elevates the Hb level significantly.
3. There is no effect of the RTX therapy on the other blood tests (WBC, renal function test, liver function test) in RA patients.

Keywords: RA, chronic, inflammatory, RF, RTX

Introduction
Rheumatoid arthritis (RA) is chronic inflammatory systemic disease that affect synovial membrane of peripheral joints leading to loss of daily function because of pain and fatigue and it is one of the leading causes of joint deformity and inability [1].

Treatment for RA:-
1. Simple analgesics and Non steroidal Anti-inflammatory drugs (NSAIDs)
2. Disease-modifying anti-rheumatic drug (DMARD) therapy in effective doses to optimally suppress synovitis [2] and effective in slowing joint destruction.
3. Corticosteroids are used as bridging therapy with DMARDS to suppress the inflammation until the DMARDs start acting [3].
4. Biologic agents which are wide group of drugs that act by different mechansim and they are used for severely active RA. RTX is one of the biological agents used for RA. Its a chimeric monoclonal antibody directed against CD20 proteins on the B cell surface used for treatment of severe active form of disease. Its control the disease activity with few side effects [4]. It was licensed in 2006 in combination with methotrexate (MTX) for the treatment of severe, active RA in adult patients with an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitors [5]. It used in RA patients seropositive for RF and/or anti-CCP antibodies using the anti-CD20 chimeric monoclonal antibody. RTX is effectively depletes B cells for up to 6–12 months. The loss of B cells is associated with improvement in RA disease activity and patients may be re-treated when the B cell compartment repopulates [6].

Bioavailability
RTX has a bioavailability of 100% after I.V infusion, acts after 6-12wks, excreted by kidney and has a half - life of 22-32 days [7, 8].

Medical uses

1. RTX used for resistant cases and for special cases of RA. It is approved as a second line after anti-TNF failure.
2. WBC cancers like non-Hodgkin lymphoma (NHL) and chronic lymphoid leukemia (CLL).
3. Severe cases of systemic lupus erythematosus (neurological and hematological)
4. ANCA associated vasculitis (1st line if cyclophosphamide is contra-indicated, in refractory or relapsing disease and in pediatric ANCA –associated vasculitis
5. Refractory polymyositis

Dose of RTX and administration in RA

Use 1000 mg IV infusion, repeat after 2 week (2 infusions separated by 2 week is 1 course). Repeat course q24weeks or based on clinical evaluation (but no sooner than 16 weeks). Used in combination with methotrexate. Premedicate with glucocorticoids 30 minutes before infusion to reduce infusion reaction to RTX. Not to exceed 1000 mg/dose.

Precautions

1. Fatal infusion reaction [9].
2. Mucocutaneous reactions (Severe) like Stevens-Johnson syndrome, and toxic epidermal necrolysis.
3. Reactivation of hepatitis B virus (HBV) infection reported, including deaths.

Side effects

Common side effects of Rituximab : headache, stomach pain, diarrhea, chills, nasopharyngitis and other upper respiratory tract infections, flashing, night sweat, urinary infection, dizziness, joint or muscle pain, itching**,** cough, rash, wheeze**,** swelling legs, fever, arthralgia, hypertention [9] Rarely it cause Thrombocytopenia [10], Renal toxicity and Tumor lysis syndrome [11].

Pregnancy and RTX

There was not enough data to evaluate effects of various doses of rituximab or the use as induction or maintenance therapy [12]. Current data suggest that the risks of treatment may be outweighed by the benefits to the mother. Possible effects:

1. congenital anomalies (club foot)
2. preterm labor (Oligohydramnios)
3. infections in pregnant mother
4. neonatal infections [12]

Aims of this study

To study the changes of the blood tests in patients with active RA after receiving four doses of RTX over a period of six months and blood samples were taken at each visit.

Patients and Methods

This was an open labeled single group longitudinal study that was conducted over 19months period. The effects of Rituximab on blood values (like ESR, ACPA,RF, Hb, WBC, SGOT, SGPT, Scr, blood urea) were demonstrated in this study on 65 RA patients receiving RTX in the Rheumatology ward in Baghdad Teaching Hospital between June 2015 and January 2017. All patients diagnosed as RA by a rheumatologist according to ACR criteria 2010 for RA. All patients had moderately to severely active disease. All the included patients were given RTX 1g (2 vials 500mg) I.V infusion for 2 cycles (6months apart), each cycle have 2 doses (2 weeks apart). Methylprednisolone 100mg infusion in 250 cc N/S, allermine ampoule 10mg and paracetamol tab. 1gm half an hour before the RTX. For each patient, a baseline data were collected during the first visit and after 2 weeks and all the participants were seen after 6 months and after 2 weeks (4 visits). During these subsequent visits, blood samples were taken. Lab. data which include RF, ACPA (at the first and last visit). Hemoglobin (Hb) level, white blood cell (WBC) count, ESR, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea and creatinine levels (at each visit). The data of the 65 patients in this study were entered into and analyzed by the statistical package for social science (SPSS) software version 17. The effect of RTX on the laboratory tests of the patients was analyzed using Chi square test(X2). A level of significance (p value) of ≤ 0.05 was considered significant.

Results

The effect of rituximab on the laboratory tests of the patients was analyzed using Chi square test(X2).The results was not significant except for the level of Hb., which increased significantly with the time($p < 0.005$). Table 1.

Table 1: The changes in the laboratory tests of the patients during the follow up period

		N	Mean	Std. Deviation	Std. Error	P value
Hb(g/dl)	First visit	64	11.0381	1.58686	.20153	
	Second visit	64	11.3489	1.42958	.18156	P<0.005
	Third visit	61	11.9549 ab	1.19029	.14975	
	Fourth visit	45	11.9711 ab	1.30554	.19909	
WBC(cell/mcl)	First visit	64	8.1774	2.75749	.35020	
	Second visit	64	7.9403	2.66461	.33841	NS
	Third visit	61	7.6373	2.43182	.31660	
	Fourth visit	44	7.6093	2.71660	.41428	
Bl.Ur(mg/dl)	First visit	63	30.8328	11.41923	1.46208	
	Second visit	63	28.6380	8.36918	1.07156	NS
	Third visit	59	29.5940	10.62133	1.40683	
	Fourth visit	40	30.0949	8.45477	1.35385	
S.Cr.(mg/dl)	First visit	62	.6817	.25143	.03246	
	Second visit	63	.6920	.17176	.02199	NS
	Third visit	58	.9911	1.36612	.18256	
	Fourth visit	38	.7442	.25521	.04196	
SGOT(iu/l)	First visit	64	20.0174	10.49672	1.33308	
	Second visit	63	21.4170	9.89135	1.26646	NS
	Third visit	58	21.9429	12.32098	1.64646	

	Fourth visit	39	19.2179	7.82289	1.26904	
SGPT(iu/l)	First visit	64	21.7194	12.39288	1.57390	
	Second visit	63	21.3713	12.31440	1.57670	NS
	Third visit	57	23.5714	14.11364	1.88601	
	Fourth visit	38	20.5263	10.13086	1.64344	

a: Significant difference from the first visit
b: Significant difference from the second visit
NS: No significant difference between visits (P>0.05)

The significant increasing in the Hb level of the patients after the treatment with RTX was represented in the following figure

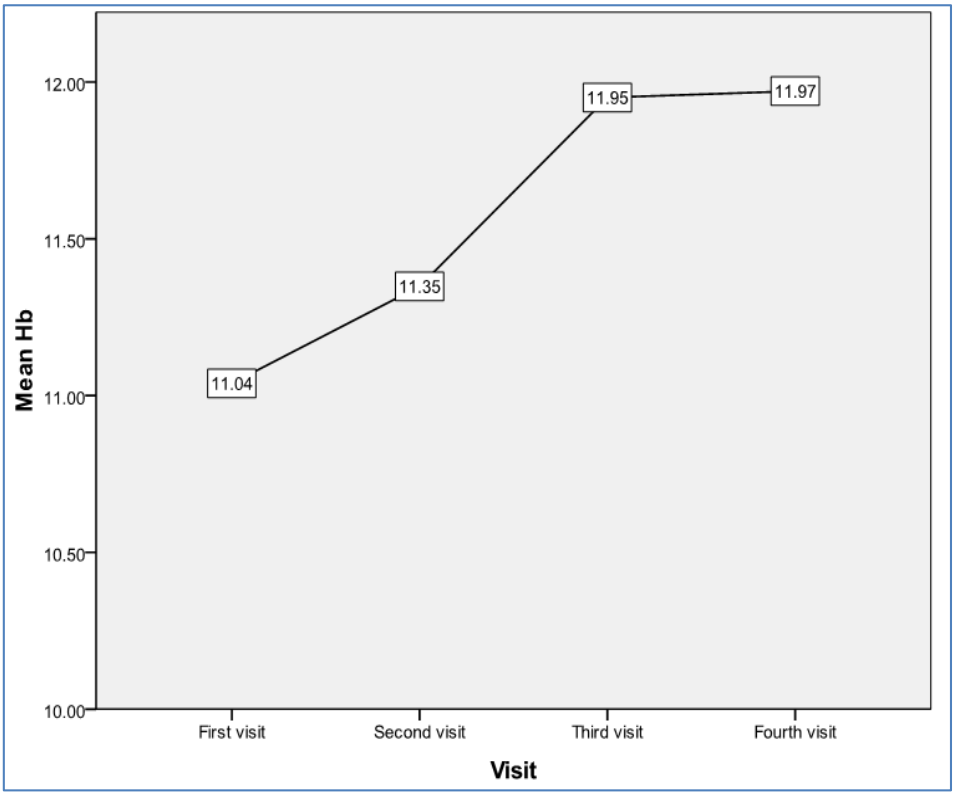

Fig 1: The effect of RTX on the blood Hb in the RA patients on RTX.

The correlation between the response to treatment and the patient serum positivity to RF and ACPA were studied as in the following table

Table 2: The correlation between the response to treatment with RTX and the patient serum positivity to RF and ACPA

RF	**+ve**	**41**	**-53.6841**	**23.82826**	**4.27968**	**P = 0.183**
RF	-ve	9	-41.2704	26.12977	8.70992	
ACPA	+ve	46	-46.4652	26.49982	3.90719	P = 0.120
ACPA	-ve	12	-55.9786	21.97460	6.94898	

The changes in the serum ACPA level before and after the treatment were analyses as in the following table 3.

Table 3: Paired Samples Statistics.

		Mean	**N**	**Std. Deviation**	**Std. Error Mean**	**P value**
Pair 1	ACCP1	167.6000	20	171.90646	38.43945	0.01
	ACCP2	62.9200	20	55.36826	12.38072	Significant

There is significant decreasing in the serum level of ACPA with the use of RTX in the RA patients participate in our study as shown in this figure

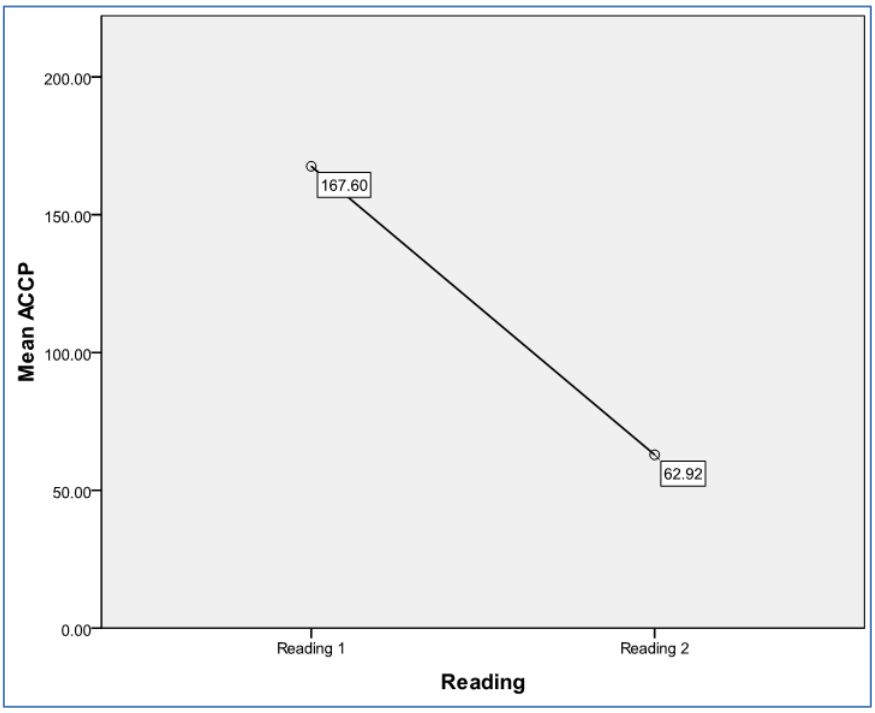

Fig 2: The significant decreasing of serum ACPA of RA patients treated with RTX.

Discussion

Safety concerns associated with many drugs indicated for the treatment of RA can be attenuated by the early identification of toxicity through laboratory monitoring [13]. For RTX we send the patient for WBC, liver transaminases, serum creatinine, blood urea, Hb, ESR, at each visit and we recommend RF and ACPA to study the relation between the seropositivity and the response to RTX In this study we also test the serum level of ACPA before and after the treatment and the decreasing of ACPA level with the treatment was significant. The effect of RTX on renal functions were not significant, although Keiichi Sumida said the biologic agent use was independently associated with lower risk of incident chronic kidney disease [14]. The effect of RTX on the liver was not significant in our study but a research published on the National Library of Medicine show mild to moderate serum liver enzymes elevations are common(15%)during RTX therapy but are self - limited. Few cases report acute liver injury with jaundice [15]. For RTX, continued monitoring of complete blood counts is recommended at 2-4 months intervals during RTX therapy as the International Journal of Rheumatology published on 2017 [13]. In our study, we recommend complete blood count 4 times per 6 months.

Conclusions

1. The use of RTX for 6 ms decreases the disease activity by decreasing serum ACPA level and ESR.
2. The use of RTX for 6 ms elevated the Hb level significantly.
3. There is no effect of the RTX therapy on the other blood tests (WBC, renal function test, liver function test and RF) in RA patients

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