PAkistan RItuximab Study

The PARIS Study

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PARIS in Pakistan !

A study of the effects of Rituximab in Pakistani patients with rheumatoid arthritis non-responsive to standard DMARD therapies.

Main Investigators

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Disclosures

- This study was carried out with help of a research grant to all investigators by Roche Pharmaceutical Company (Pakistan) Ltd.

- All treatment-related expenses were borne by patients themselves

The Natural History of RA

- **Outcome After 40 Years with Rheumatoid Arthritis: A Prospective Study of Function, Disease Activity, and Mortality**

  NICOLA J. MINAUR, RICHARD K. JACOBY, JOHN A. COSH, GORDON TAYLOR, and JOHANNES J. RASKER

- Journal of Rheumatology 2004

RA Outcome at 40 Years --- Starting 1957

- **86% had died ……. Mainly from cardiovascular disease**
  - 13% deaths directly attributed to RA
  - 47% had severe physical disability before death

Of the remaining 14%, half had severe physical disability whereas at the beginning only 11% of these had severe disability

Rituximab

- A designed monoclonal antibody acting to prevent the action of B lymphocytes bearing the CD20 molecule
- First used in 1993 against B-cell lymphoma
- Now used to treat various other autoimmune diseases also

Primary Objective

To determine the percentage of RA patients achieving improvement in their disease activity level post-treatment with rituximab at 6 months using DAS-28 as an index.

Secondary Objectives

- To determine the percentage of RA patients achieving improvement in their disease activity level post treatment at 12 months interval using DAS-28
- To determine the safety profile of rituximab in Pakistani RA population
- Evaluation of response at 6 and 12 months using ACR 20/50/70 and EULAR response criteria

Efficacy Measures Used

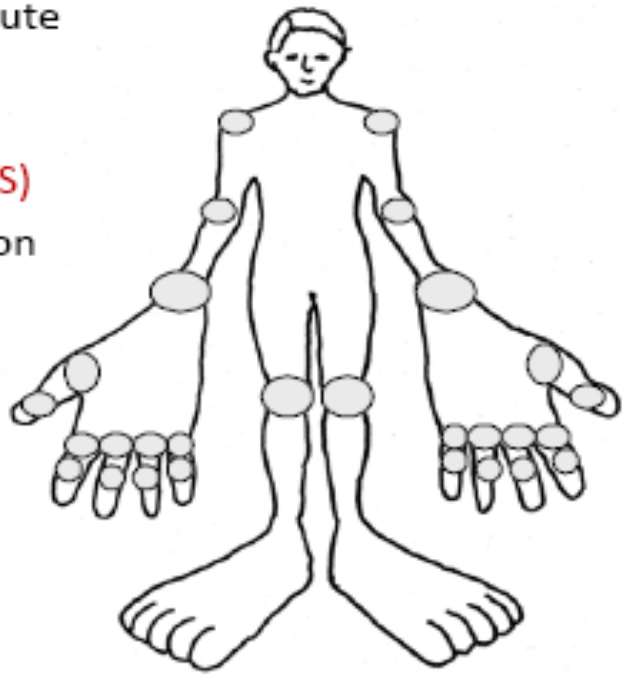
- Disease Activity Score 28 (DAS 28) measuring the clinically detectable inflammation at 28 selected joints.
- EULAR criteria for measuring RA disease activity.
- American College of Rheumatology criteria for level of improvement from base line (ACR 20/50/70)

DAS28: A Simplified Disease Activity Score

- Simplified disease activity score using 28-joint count
  - Integrates measures of physical examination, acute phase response, and patient self-assessment

$$DAS28 = 0.56\sqrt{\text{Tender 28}} + 0.28\sqrt{\text{Swollen 28}} + 0.70\ln(\text{ESR}) + 0.014\,(\text{Global Health on VAS})$$

- Provides absolute indication of RA disease activity on a scale of 0.49 to 9.07
  - DAS28 >5.1 = *high* disease activity
  - DAS28 3.2-5.1 = *moderate* disease activity
  - DAS28 2.6-3.2 = *low* disease activity
  - DAS28 <2.6 = *remission*



AM van Gestel et al. *Arthritis Rheum*. 1998;41(10):1845-50.

Efficacy Criteria

- Disease remission:
  DAS 28 score < 2.6

- Low disease activity:
  DAS 28 score between 2.6 and 3.2

EULAR Response Criteria for RA:
Continuous Variable to Dichotomous Benchmark

DAS28 at endpoint	Improvement in DAS28 from baseline		
	>1.2	>0.6 and <1.2	<0.6
<3.2	Good	Moderate	None
3.2-5.1	Moderate	Moderate	None
>5.1	Moderate	Moderate	None

AM van Gestel et al. *Arthritis Rheum.* 1996; 39:34-40.

ACR Response Criteria: The Traditional Dichotomous Benchmark

- Reported as % improvement, comparing disease activity at two discrete time points
  - ACR20 is ≥ 20% improvement
  - ACR50 is ≥ 50% improvement
    - ACR50 responders include ACR20 responders
  - ACR70 is ≥ 70% improvement
    - ACR70 responders include ACR20 & ACR50 responders
- Used to maximally discriminate effective treatment from placebo treatment in clinical trials
- Not directly applicable to clinical practice

DT Felson et al. *Arthritis Rheum.* 1995;38(6):727–735.

Study Design & Patient Population

- Phase IV
- Open label
- Single arm
- Multicentre trial
- Planned enrolment of 80 patients
- 5 centers across Pakistan

Study Timelines

- Start date: January 2010
- Finish date: June 2011
- 75 patients successfully recruited
- Final analysis derived from data of 74 patients that have completed the 12-month assessment
- Submission for publication is expected in Q4 2012

Patient Selection

Inclusion Criteria

- Able and willing to give written informed consent
- Men and women aged 18-80 years
- Patients with a diagnosis of at least 6 months duration with presence of 4 features as per ACR criteria
- DAS-28 score $\geq$ 3.70 at baseline
- Inadequate response to MTX taken for at least 12 weeks with at least 4 weeks of having been on a stable dose of 15 mg/week prior to enrolment

Patient Selection

Inclusion Criteria

- A stable dose of glucocorticosteroids (≤ 10 mg/day prednisone or equivalent) permitted
- Use of NSAIDs permitted if stable dose for at least 2 weeks prior to baseline
- Patients of reproductive potential (males and females) willing to use a reliable method of contraception (e.g. contraceptive pill, IUD, physical barrier) during the study and for 12 months after last Rituximab administration
- If female and of childbearing potential, a negative serum pregnancy test within 2 weeks prior to baseline

Patient Selection

Exclusion Criteria Related to RA

- Bed bound or wheelchair bound patients
- Rheumatic autoimmune disease other than RA, or significant systemic involvement secondary to RA
- Diagnosis of juvenile idiopathic arthritis (JIA), also known as juvenile rheumatoid arthritis (JRA)

Patient Selection

Exclusion Criteria Related to Medications

- History of severe allergic or anaphylactic reactions to a biological agent or known hypersensitivity to any component of rituximab or to murine proteins
- Previous treatment with any approved or investigational biologic agent for RA
- Concurrent treatment with any biologic agent for any indication
- Receipt of any vaccine within 4 weeks prior to baseline
- Contraindications of parenteral glucocorticoids and drugs required for the treatment of adverse event secondary to rituximab therapy
- Intra-articular or parenteral glucocorticoids within 4 weeks prior to baseline

Patient Selection

Exclusion Criteria Related to General Health

- Known active and/or severe infection or any major episode of infection requiring hospitalization or treatment with IV anti-infectives within 4 weeks prior to baseline
- History of serious recurrent or chronic infection
- Primary or secondary immunodeficiency
- Pregnancy or breast feeding
- Known history of active cancer during the past 5 years
- Currently active alcohol or drug abuse or history of alcohol or drug abuse within 24 weeks prior to baseline

Patient Selection

Exclusion Criteria Related to Lab Findings

- Positive serum human chorionic gonadotropin measured prior to the first infusion of study drug
- Positive test for hepatitisB or C serology
- Positive HBcAb associated with positive HBV detection (> 29 IU/L or > 169 copies/mL)
- Hemoglobin < 8.0 g/dL
- Absolute neutrophil count < 1.5 × 103/μL
- Concentration of serum IgG and/or IgM below 5.0 and 0.40 mg/mL, respectively

Demography (N=74)

Variables	Mean ±S.D	
Age (years)	43.3 ± 10.9	
Gender	n	(%)
Male	15	20.3
Female	59	79.7
RF / anti-CCP Positive	67	90.5

RA Features

Variable	n	(%)
Morning stiffness	60	81.1
Wrist and finger joint inflammation	72	97.3
Large join inflammation	71	95.9
Characteristic Distribution for IJD	72	97.3
First degree relative with IJD	1	1.4
Clinical evidence of synovitis	71	95.9
Malaise / Fatigue	66	89.2
Occasional Fever	1	1.4

Results at 6 months

Variables	Baseline Mean±S.E.M	Six Month Mean±S.E.M	Mean Difference	P-value	95% C-I
ESR	43.8 ± 28.9	30.35 ± 19.1	13.4	<0.01	6.9 – 20.0
VAS	71.1 ± 20.3	36.9 ± 24.6	34.2	<0.01	27.9 – 40.5
SJC	11.2 ±8.6	2.4 ±2.9	8.5	<0.01	6.9 – 10.5
TJC	17.6 ±8.2	6.0 ±6.4	11.6	<0.01	9.6 – 13.5
DAS 28	6.6 ± 1.2	4.3 ± 1.7	2.3	<0.01	1.9 – 2.7

Results at 6 months (Cont....)

Variables	Baseline Mean±S.E.M	Six Month Mean±S.E.M	Mean Difference	P-value	95% C-I
Pain	71.1 ± 19.3	35.8 ± 24.9	35.3	<0.01	29.6 – 40.9
Health Assessment Questionnaire	9.6 ± 4.9	3.8 ± 4.6	5.8	<0.01	4.2 – 7.4

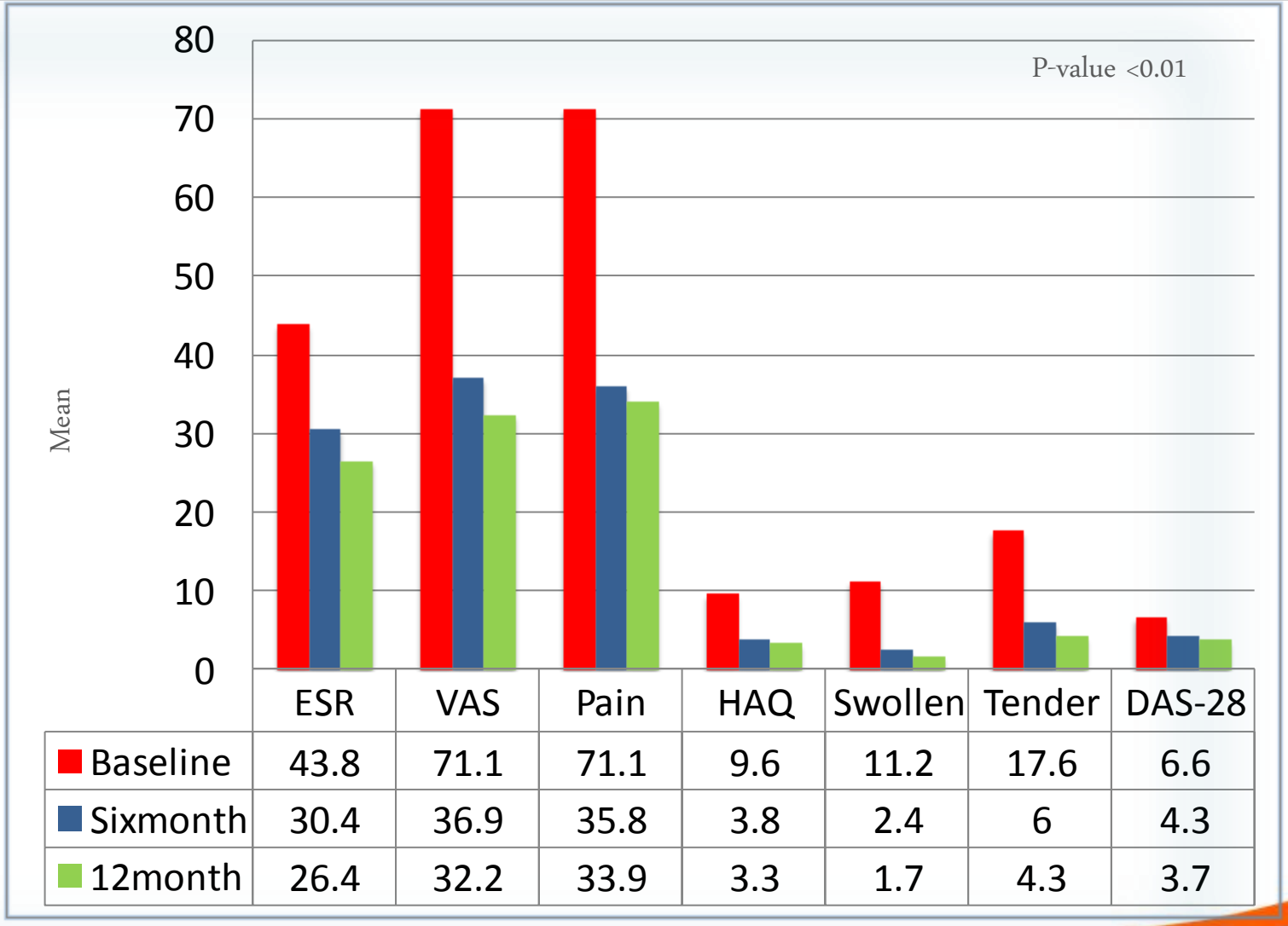
Results at 12 Months

Variables	Baseline Mean±S.E.M	12 Month Mean±S.E.M	Mean Difference	P-value	95% C-I
ESR	43.8 ± 28.9	26.38 ± 17.6	17.4	<0.01	11.5 – 24.6
VAS	71.1 ± 20.3	32.2 ± 24.1	38.9	<0.01	33.8 – 46.9
SJC	11.2 ± 8.6	1.7 ±2.8	9.4	<0.01	7.2 – 11.6
TJC	17.6 ± 8.2	4.3 ± 5.7	13.4	<0.01	11.5 – 15.4
DAS 28	6.6 ± 1.2	3.7 ± 1.4	2.9	<0.01	2.5 – 3.3

Results at 12 Months

Variables	Baseline Mean±S.E.M	12- Month Mean±S.E.M	Mean Difference	P-value	95% C-I
Pain	71.1 ± 19.3	33.9 ± 23.1	37.2	<0.01	30.8 – 43.6
Health Assessment Questionnaire	9.6 ± 4.9	3.3 ± 3.5	6.3	<0.01	4.9 – 7.9

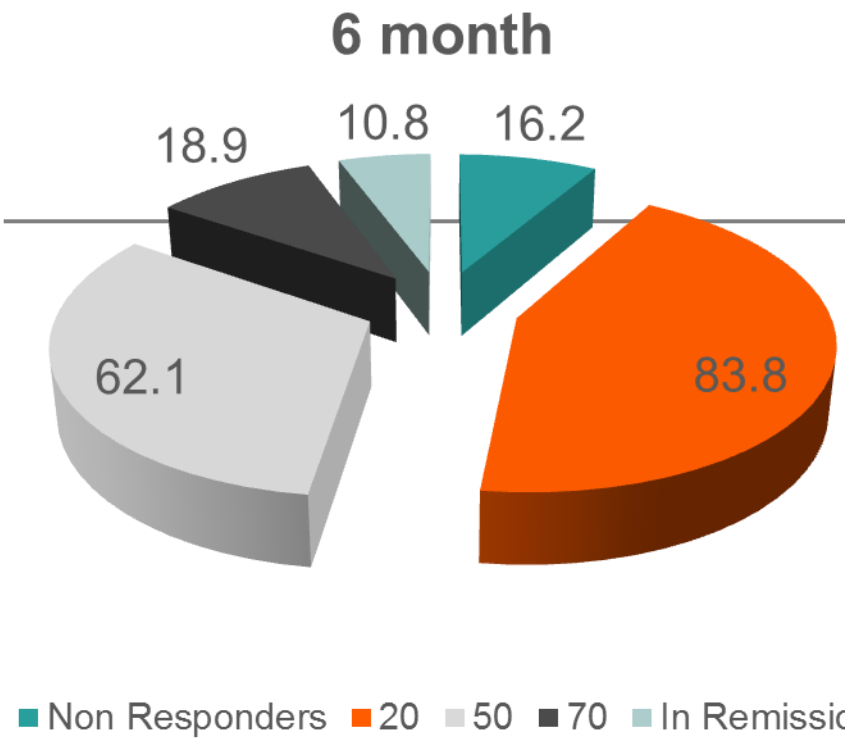
Comparison at 0, 6 & 12 Months

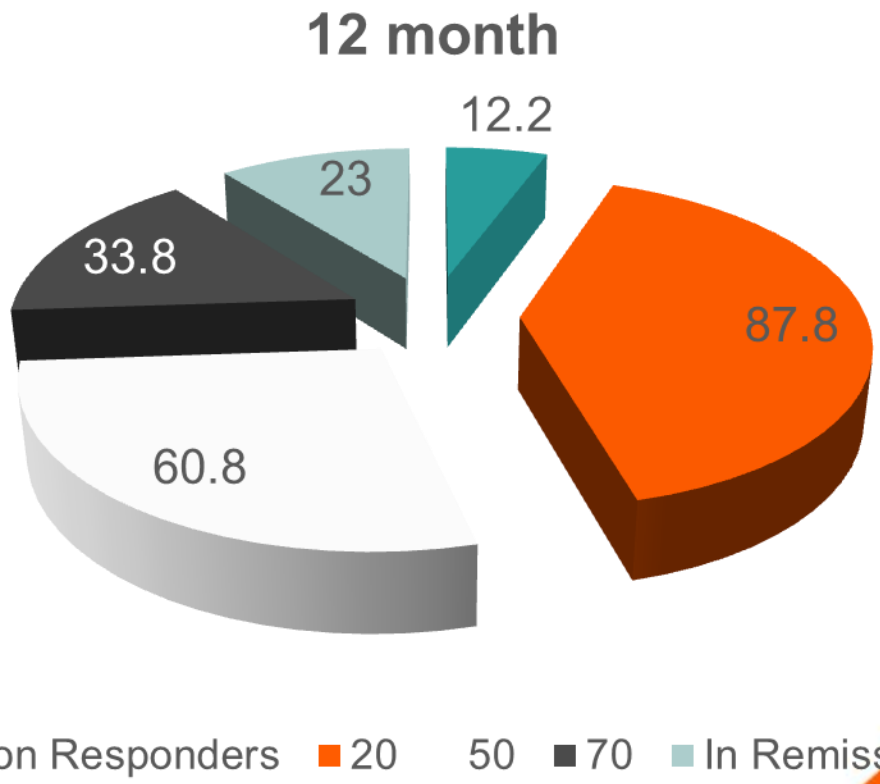


	ESR	VAS	Pain	HAQ	Swollen	Tender	DAS-28
Baseline	43.8	71.1	71.1	9.6	11.2	17.6	6.6
Sixmonth	30.4	36.9	35.8	3.8	2.4	6	4.3
12month	26.4	32.2	33.9	3.3	1.7	4.3	3.7

ACR Criteria Response

	6 months		12 months	
Level	n	(%)	n	(%)
Non Responders	12	16.2	9	12.2
20	62	83.8	65	87.8
50	46	62.1	45	60.8
70	14	18.9	25	33.8
In Remission	10	10.8	18	23.0


6 month
18.9
10.8
16.2
62.1
83.8
Non Responders
20
50
70
In Remission


12 month
12.2
23
33.8
87.8
60.8
Non Responders
20
50
70
In Remission

EULAR Response Criteria – Baseline

DAS-28	
>5.1	≤5.1 and >3.7
64 (86.5%)	10 (13.5%)

EULAR Response Criteria – 6 Months

	DAS-28	
Change in DAS-28	>5.1	≤5.1 and >3.7
>1.2	50 (Good)	7 (Good)
>0.6 and ≤1.2	12 (Moderate)	2 (moderate)
≤0.6	2 (None)	1 (None)

EULAR Response Criteria – 12 Months

	DAS 28	
Change in DAS-28	>5.1	≤5.1 and >3.7
>1.2	52 (Good)	4 (Good)
>0.6 and ≤1.2	6 (Moderate)	4 (Moderate)
≤0.6	6 (None)	2 (None)

DAS at 0, 6 & 12 Months

	≤ 2.6	> 2.6
Base Line	0	74
6 Month	10	64
12 Month	18	56

ESR at 6 and 12 Months

ESR	Baseline	6th month	12th month
Male			
0 - 14	4	9	11
> 14	11	6	4
Female			
0 - 20	39	49	52
>20	20	10	07

Safety

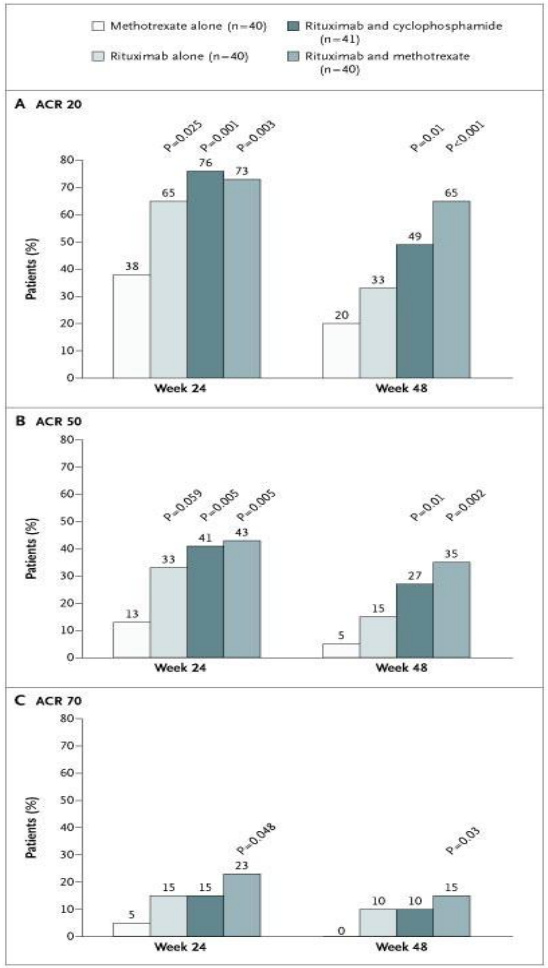
Adverse Events	No. of patients
Fever	4
Headache	2
Cough	1
Runny nose	2
Indigestion	1
Diarrhea	2
Itching	1
Fever+Breathing difficulty	11
Chills	1
Anorexia	3
Dizziness	4
Shivering	1
Fever+vomiting	2
Fever+Runny nose	1

No **Serious Adverse Event** was reported during the course of the study

Mild-Moderate with Probability

Efficacy of B-Cell–Targeted Therapy with Rituximab in Patients with Rheumatoid Arthritis; Edwards JCW et al; NEJM; June 2004

Response	24 wks	48 wks
ACR 20	73% (84)	65%
ACR 50	43% (62)	35%
ACR 70	23% (19)	15%



Comparative Results at 6 Months

Criteria	PARIS – 2011 %	REFLEX – 2006 %	DANCER – 2006 %
ACR 20	84	51	54
ACR 50	62	27	34
ACR 70	19	12	20

Conclusions

- **Better than expected efficacy of rituximab in Pakistani patients with RA not responding to standard DMARD therapy.**
- **Results at 12 months even better than at 6 months.**
- **No serious adverse events .**
- **Easily tolerated by all patients**

Critique

- **Sample size much smaller than previously conducted studies hence validity of results open to discussion.**

- **Psychological profile of Pakistani patients perhaps contributed to significant improvement in VAS score and hence final DAS 28 score.**

Serene as the Seine in Paris with Rituximab in Pakistan

THANK YOU

Back-up Slides

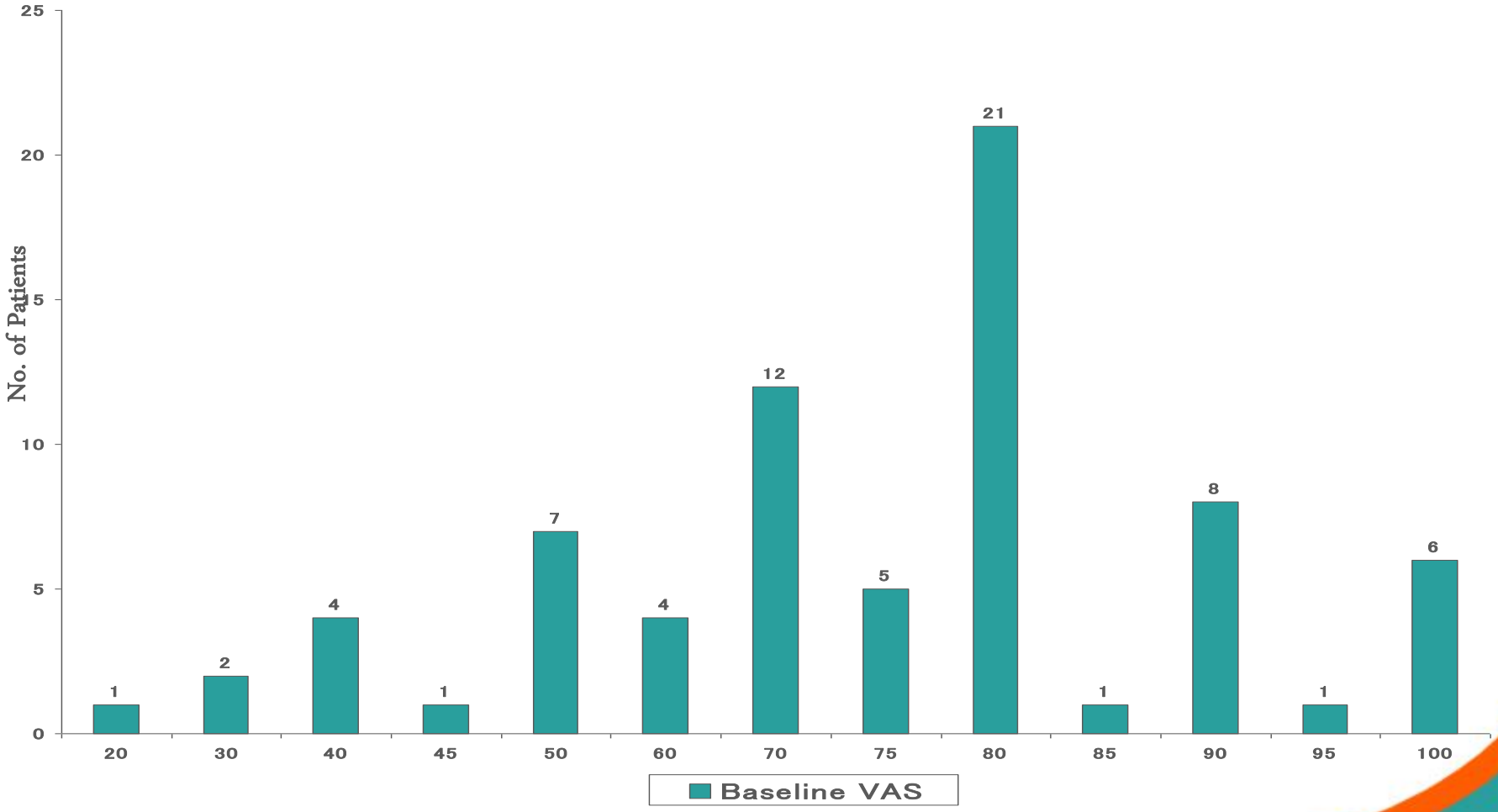
Concomitant Illness & Medication

Variables	n	(%)
Diabetes	4	5.4
Diabetes+HTN	2	2.7
Hypertension	11	14.9
HTN+Osteoporosis	1	1.4
HTN+Osteoporosis+Osteoarthritis	1	1.4
HTN+Blood disorder	3	4.1
Osteoporosis	6	8.1
Osteoporosis+Osteoarthritis	1	1.4
Osteoarthritis	2	2.7
Concomitant illness	31	41.9
Concomitant Medication	44	59.5

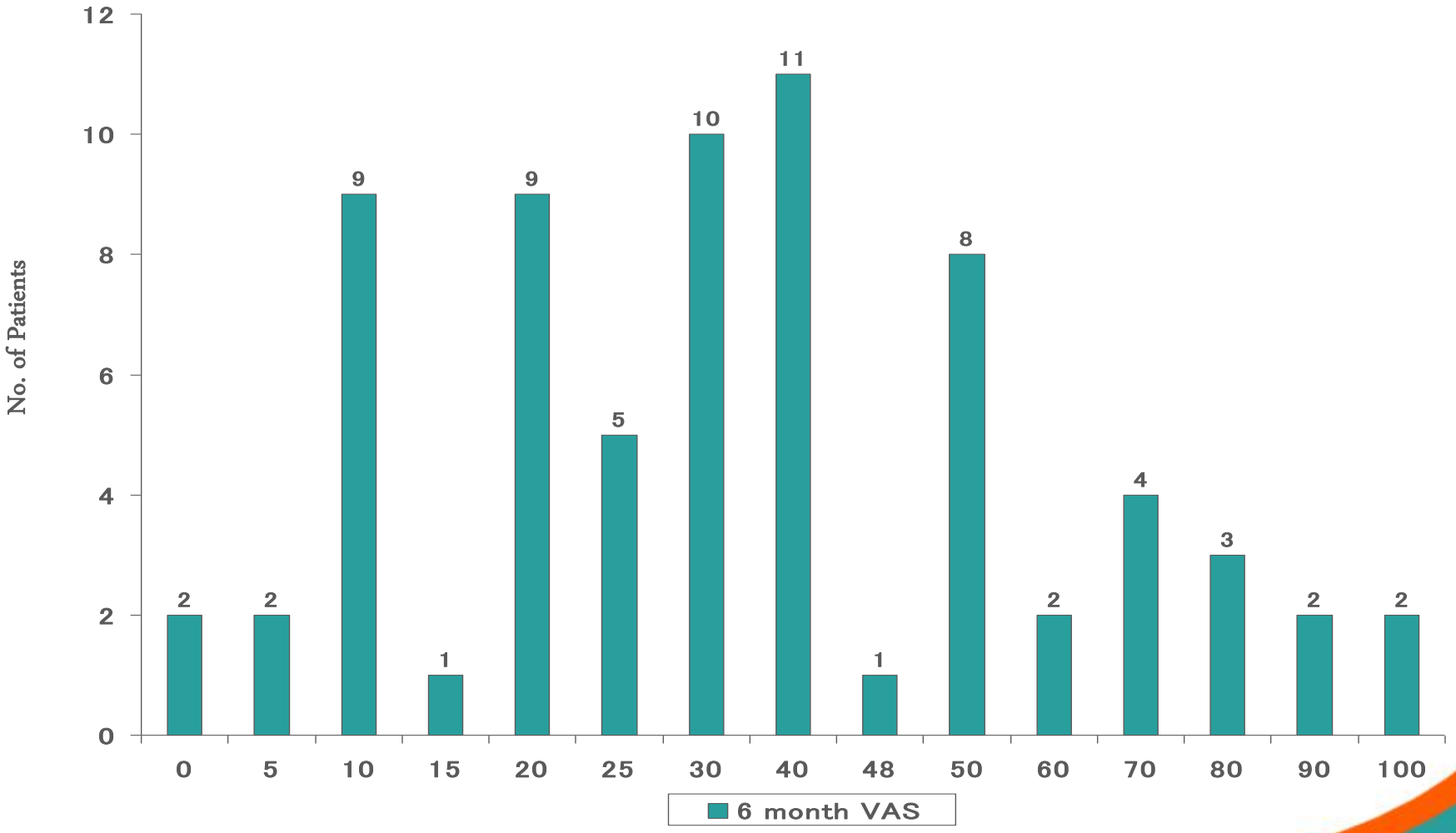
Concomitant Illness & Medication (Back up Slide)

Variables	n	(%)
Diabetes	6	8.1
Hypertension	18	24.3
Blood disorder	3	4.1
Osteoporosis	9	12.2
Osteoarthritis	4	5.4
Concomitant illness	40	54.1
No Concomitant illness	34	45.9
Concomitant Medication	44	59.5

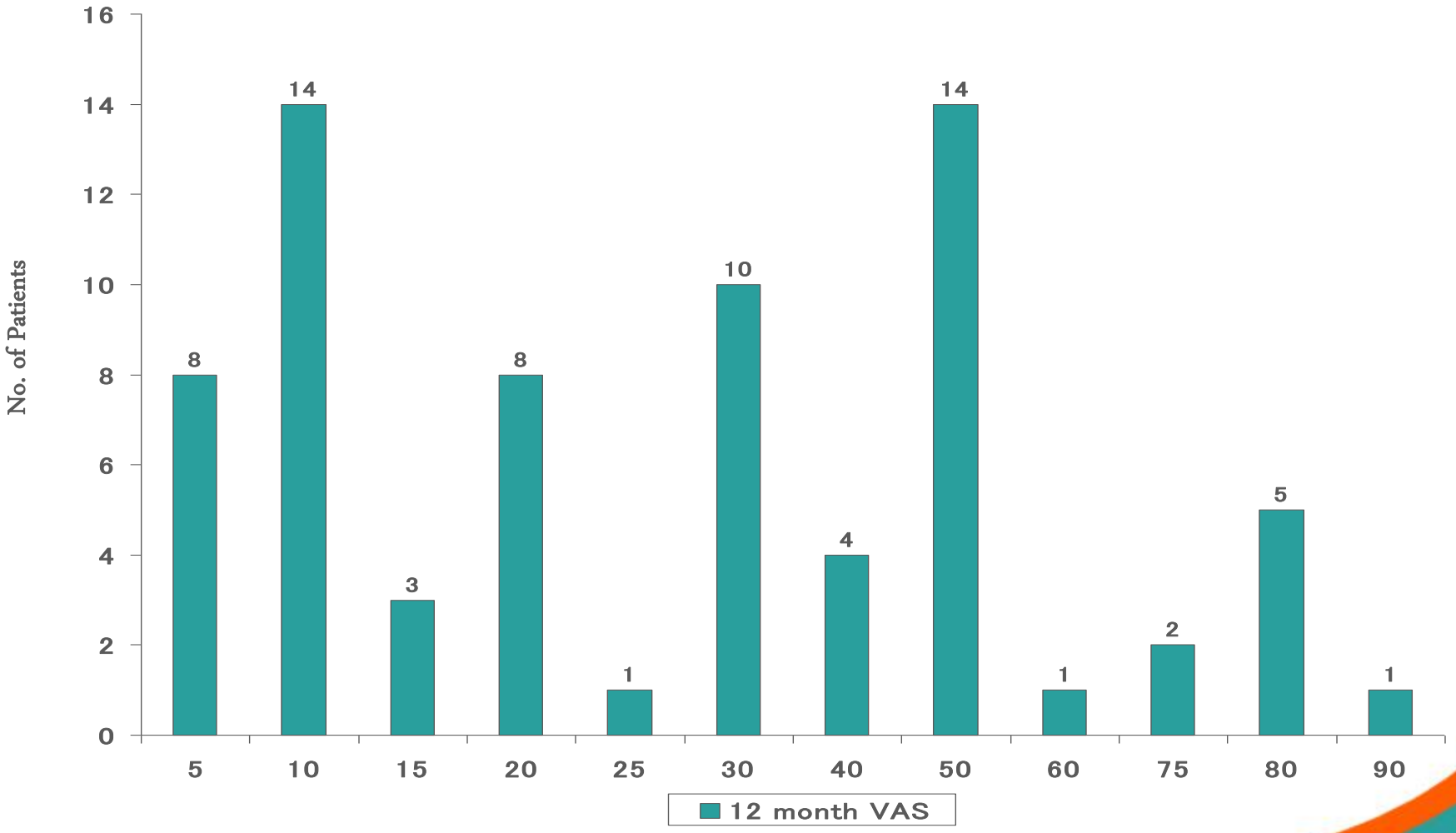
Baseline VAS



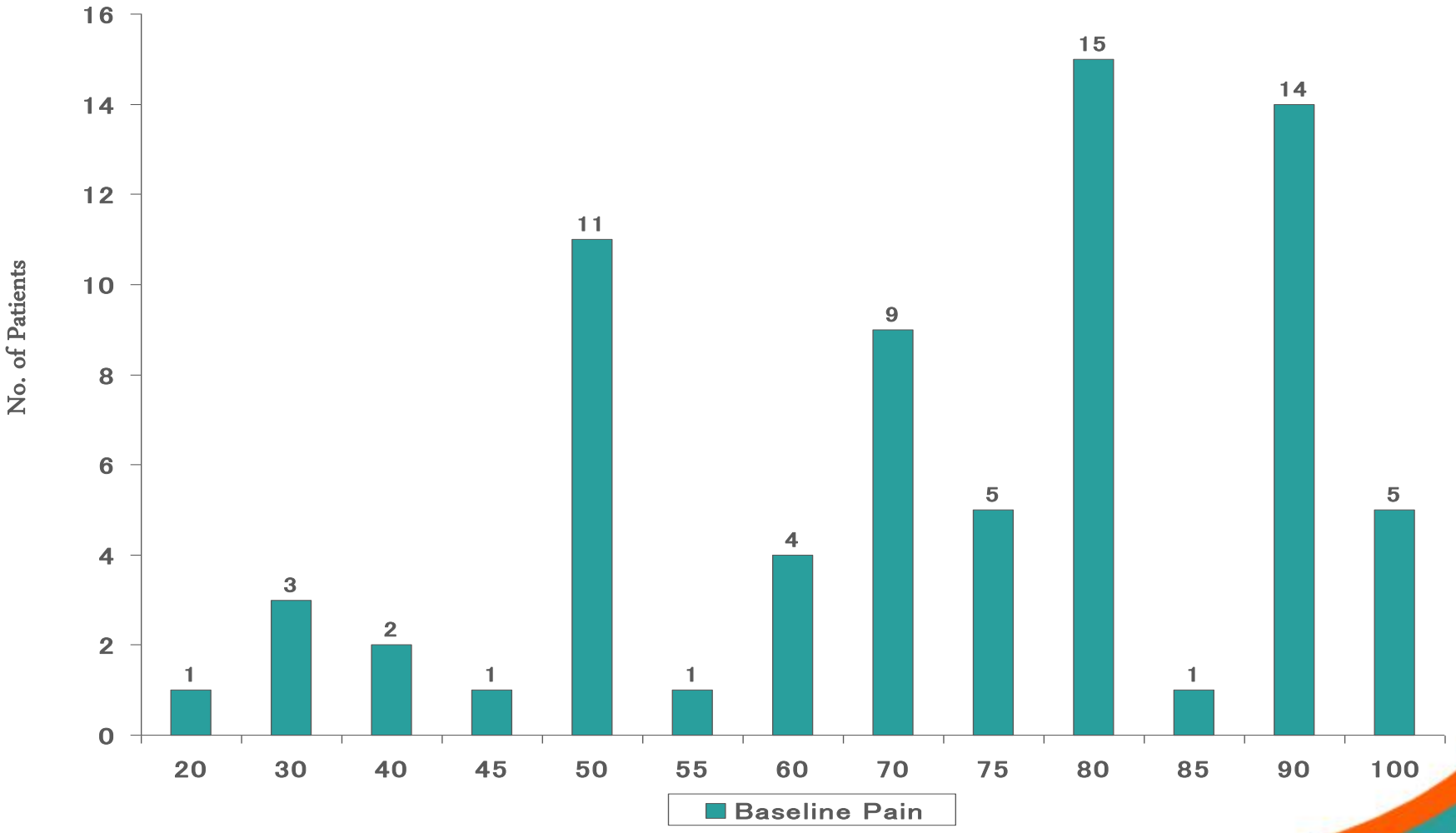
6th month VAS



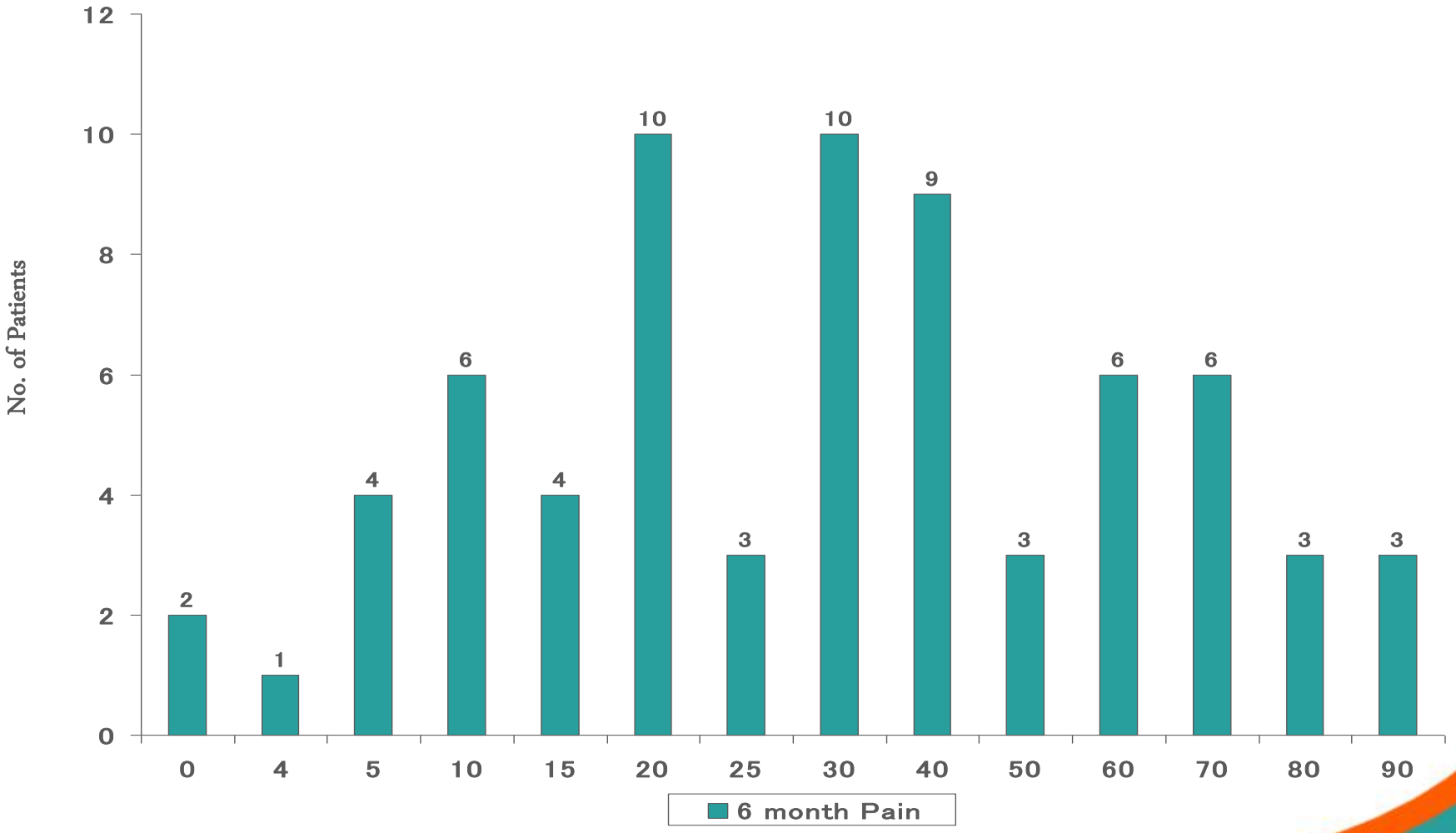
12th month VAS



Baseline Pain



6 month Pain


No. of Patients
12
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6 month Pain

12 month Pain