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Comparison Study between Real Life and Published Data Outcome among Myelofibrosis Patients Who are Using Ruxolitinib at King Abdulaziz Medical City-Central Region

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ABSTRACT

Objectives: *The aim of this study is to evaluate the efficacy and safety of Ruxolitinib among Myelofibrosis patients in real life compared to published data.* ***Methods:*** *In this retrospective observational chart review study we reviewed the medical records for all patients diagnosed with Myelofibrosis in King Abdulaziz Medical City who has received Ruxolitinib from March 1, 2012-December 1, 2015. The efficacy and safety results of Ruxolitinib were compared with published data.* ***Results:*** *A total of 20 patients were included. The average age was 63.3 (SD=11.6) years, with 55% of females. Efficacy: At week 24, only 20% of the study participant achieved spleen size reduction equal to or more than 20% with total average of 8% reduction in the spleen size as compared to 31.60% in COMFORT-1 study ($p \leq 0.001$), The highest symptoms reduction observed with fatigue and bone pain (45% and 40% of the affected patients respectively) followed by Abdominal distress (35%) whereas no statistically significant difference observed in early satiety and night sweat. Weight loss showed improvement in 15% of the patients. Safety: Fatigue was observed in 45% of the patients, diarrhea (5%), dyspnea (15%), dizziness (5%), nausea (5%), constipation (10%), vomiting (5%), pain in extremities (5%), arthralgia (5%), pyrexia (5%), and abdominal pain (35%). At week 24, Platelet count decreased by 26% and hemoglobin decreased by 5% from the baseline. In general, only three reported cases for temporal or permanent drug discontinuation.* ***Conclusion:*** *Ruxolitinib therapy in real life as compared to published trials was associated with significant improvement in Myelofibrosis related symptoms and splenomegaly with an acceptable safety profile.*

Keywords: Myeloproliferative neoplasms, Myelofibrosis, Ruxolitinib, Safety, Efficacy

Abbreviations: MPN: Myeloproliferative Neoplasms; PV: Polycythemia Vera; ET: Essential Thrombocythemia; PMF: Primary Myelofibrosis; JAK-STAT: Janus Kinase/Signal Transducer and Activator of Transcription; MF: Myelofibrosis; NGHA: National Guard Health Affairs; QCPR: QuadraMed; EMR: Electronic Medical Records System; TSS: Total Symptom Score; VTE: Venous Thromboembolism; SD: Standard Deviation; IQR: Interquartile Range; WBC: White Blood Cell; HGB: Hemoglobin

INTRODUCTION

Myeloproliferative neoplasms (MPN) are stem cell-derived clonal myeloid malignancies. The BCR-ABL1-negative MPN includes polycythemia vera (PV), essential thrombocythemia (ET), and Primary Myelofibrosis (PMF). In 2005, the discovery of dysregulated Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathway in patients with MPN have increased the interest in developing molecularly targeted therapies that will act by inhibiting the mutated JAK. Ruxolitinib is a potent oral JAK1 and JAK2 inhibitor that has been studied in patients with PV, ET, and PMF [1]. Most of the patients with MPN report to the clinic with anemia or splenomegaly symptoms

such as an abdominal distress and as the disease get worse the patient become more symptomatic due to bone marrow deterioration where the most frequent symptoms of the Myelofibrosis (MF) are night sweats, weight loss, bone pain, and thrombosis [2].

Treatment of the MF can be started by improving the symptoms to improve the quality of life of the patient such as anemia and splenomegaly. To assess anemia, all treatable causes like iron deficiency and vitamin B12 deficiency must be excluded. Coomb's test can be helpful sometimes, as its positive result might indicate hemolysis where corticosteroids are the drug of choice in such rare cases. Most of the patients will need treating agents for their anemia [2]. Patients who received hydroxyurea to treat symptomatic splenomegaly showed a 40% response rate [3]. Splenectomy can be a treatment option in extremely large and drug therapy refractory cases of splenomegaly [2]. JAK2 rearrangement and activation are major characteristics of MF, Ruxolitinib improves the constitutional symptoms of the lymphoid disorder because it acts against the activated JAK2 fusion genes [4]. Ruxolitinib works by different mechanisms of action, it has a suppressive effect on dendritic cell differentiation (which will impair T-cell Activation), suppressive effect on Interleukin-12 production and normalizes the hyper-inflammation [5].

In COMFORT I study, the efficacy of Ruxolitinib was evaluated as the proportion of subjects with ≥ 35% reduction in spleen size from baseline at week 24. Ruxolitinib treated group showed a significant reduction in spleen size (41.9% *vs*. 0.7%; $p<0.001$), and almost 46% of the patients showed an improvement in the Total Symptom Score (TSS) of more than 50% [6]. In another Study by Vannucchi and his colleagues, patients who have used Ruxolitinib for the treatment of polycythemia vera *vs.* the standard therapy with hydroxyurea, had a significant decrease in their spleen volume (38% *vs.* 1%) and hematocrit control (60 % *vs.* 20 %) at week 32. In the same study, 50% reduction in the total symptom score was achieved by 49% in the Ruxolitinib group compared to 5% only in the hydroxyurea group. But Ruxolitinib was associated with a higher incidence of anemia and thrombocytopenia (2% and 5% *vs.* 0% and 4% respectively) [7]. This higher incidence of thrombocytopenia has been found to be associated with patients who have lower platelet count at baseline ($\leq 75 \times 109$ /L) and can be managed by starting with a low dose of Ruxolitinib and escalation to the recommended dose [8]. In addition, Ruxolitinib can reduce the mean hemoglobin level by around 10 g/L, but thereafter the level will be recovered to near the baseline [9].

Ruxolitinib also has been found to improve the quality of life of patients by the significant reduction in the Myelofibrosis associated symptoms such as abdominal pain, early satiety, night sweating, and bone pain [10]. But on the other hand, Ruxolitinib has some non-hematologic adverse effects including diarrhea, peripheral edema, abdominal pain, nausea, and fatigue [8].

Many clinicians are interested in published real-world trials that report the ongoing clinical practice in addition to well-controlled clinical trials [11]. The clinical research outcomes from real-world data may or may not confirm the outcomes of the trial, for example, Louis Kwong confirmed on his project about the Rivaroxaban, that real-world data of Rivaroxaban reduces the incidence of venous thromboembolism (VTE) in patients after major orthopedic surgery [12]. In contrast, Joseph, et al., found that estimated absolute survival probabilities which are obtained from the clinical trials may be optimistic in some cases [13]. One trial was conducted on Ruxolitinib in real-life international setting done by Davis, et al., found that it has a positive clinical effect on the low-risk MF patients [14]. To the best of our knowledge, there is no published local data to assess Ruxolitinib efficacy and safety in real-life settings. Therefore the aim of this study is to assess Ruxolitinib efficacy and safety in the Saudi population diagnosed with MF compared to published data.

MATERIALS AND METHODS

This is a retrospective cross-sectional observational study conducted at King Abdulaziz Medical City/National Guard Health Affairs (NGHA) in Riyadh. The study included all patients diagnosed with Myelofibrosis who has received Ruxolitinib from March 1, 2012-December 1, 2015. The data were collected from QuadraMed (QCPR) electronic medical records system (EMR) for the period from March 1, 2012-October 1, 2015 and from ''Best care'' electronic medical records system (EMR) from November 1, 2015-December 1, 2015. The efficacy and safety result of Ruxolitinib is compared with COMFORT-1 study results.

The specific objectives of this study are (1) To assess ruxolitinib efficacy in Saudi population compared with COMFORT-1 study results, efficacy indicators include spleen size, symptoms improvement rate (2) To assess ruxolitinib safety in term of most predominant side effects of ruxolitinib in Saudi population compared with COMFORT-1 study results (3)

and To determining patients tolerability to Ruxolitinib among Saudi patient population. Data extracted from (EMR) include age, gender, nationality, diagnosis, medication start date and dose, adjusted dose and adjustment date as well reason for dose adjustment in addition to hemoglobin, platelet count, WBC, spleen size (as measured by ultrasounds) and symptoms. All efficacy and safety parameters have been assessed at the beginning of the treatment and on week twenty-four and then compared with the same parameter in COMFORT-1 study.

Statistical Analysis

A descriptive statistical analysis was performed for the study sample. For continuous variables, measures of central tendency (e.g. mean, median) and standard deviation were provided. Proportions were used for categorical variables. Comparison between pre and post-treatment with Ruxolitinib in terms of numerous blood measures (WBC, HGB, and platelets) was made using the paired t-test or Wilcoxon signed-ranks test. A comparison with measures reported in other published studies was made using the t-test or Mann-Whitney U test. Statistical significance was considered at $p<0.05$. All statistical analyses were performed using SPSS 21.0 (Release 21.0.0.0, IBM, USA) and Microsoft Excel 2016.

RESULTS

A total of 20 patients were included. The average age was 63.3 (SD=11.6) years, with 55% females (Table 1). The table also includes descriptive statistics for baseline laboratory measures. Results from paired comparisons between our study and COMFORT-1 study are shown in Tables 2 and 3.

Efficacy

The results for comparing efficacy indicators were illustrated in Table 2. Spleen size-reduction measured by ultrasounds was observed in the Ruxolitinib recipient. In our study, we found that only 20% of the study participant achieved spleen size reduction equal to or more than 20% with a total average of 8% reduction in the spleen size as compared to 31.60% in COMFORT-1 study ($p \leq 0.001$). At week 24, most of the study participants experienced substantial symptoms improvement compared to COMFORT-I trial (Table 2). The highest symptoms reduction observed with fatigue and bone pain (45% and 40% of the affected patients respectively) followed by Abdominal distress (35%) whereas no statistically significant difference observed in early satiety and night sweat. weight loss showed improvement in 15% of the patients.

Safety

The results for comparing safety indicators were shown in Table 3. Safety of Ruxolitinib was assessed as the percentage of patients who developed side effects as compared to COMFORT-1 study. We have observed several side effects including fatigue, diarrhea, dyspnea, dizziness, nausea, constipation, vomiting, pain in extremities, arthralgia, pyrexia, abdominal pain, peripheral edema, ecchymosis, and insomnia. Fatigue was observed in 45% of the patients, diarrhea (5%), dyspnea (15%), dizziness (5%), nausea (5%), constipation (10%), vomiting (5%), pain in extremities (5%), arthralgia (5%), pyrexia (5%), and abdominal pain (35%). In week twenty-four Platelet count decreased by 26% and hemoglobin decreased by 5% from the baseline.

Tolerability

During the study duration (24 weeks) there were 37 dose modifications reported in study participants due to side effects as shown in Table 4 whereas three cases reported for temporal or permanent drug discontinuation due to anemia and thrombocytopenia.

Table 1 Profile of subjects-baseline measures, N=20

Factor	Value
Gender (n%)	
Male	9 (45%)
Female	11 (55.0%)
Age (year) Mean (SD)	63.3 (11.6)
Median (IQR)	66 (56.5-71.5)

Baseline Measures	
WBC Mean (SD)	14.5 (12.0)
Median (IQR)	10.6 (5.6-20.7)
HGB Mean (SD)	110.4 (27.4)
Median (IQR)	106 (86.5-135)
Platelets Mean (SD)	256.9 (263.9)
Median (IQR)	162 (91.5-361)
SD: Standard Deviation; IQR: Inter Quartile range; WBC: White Blood Cell; HGB: Hemoglobin	

Table 2 Efficacy indicators: Percentage of patients who experienced symptoms and spleen reduction in our study compared to COMFORT-I study

Efficacy Parameters	Percentage of Patients who Experienced Symptoms and Spleen Reduction		p-value
	NGHA Study	COMFORT-I Study	
Spleen Size Reduction	8%	31.60%	p<0.001
Fatigue	45%	32%	p<0.05
Bone Pain	40%	21%	p<0.001
Weight Loss	15%	Not reported	Not reported
Abdominal Distress	35%	29%	p<0.002
Early Satiety	35%	43%	p<0.062
Night Sweat	35%	42%	p<0.052
NGHA: National Guard Health Affairs			

Table 3 Safety indicators: Percentages of patients who develop adverse effects

AEs	Percentages of Patients who Developed Adverse Effects		p-value
	NGHA Study	COMFORT-I Study	
Fatigue	45	25.2	p<0.001
Diarrhea	5	23.2	p<0.001
Dyspnea	15	17.4	p<0.57
Dizziness	5	14.8	p<0.001
Nausea	5	14.8	p<0.001
Constipation	10	12.9	p<0.001
Vomiting	5	12.3	p<0.001
Pain In Extremities	5	12.3	p<0.001
Arthralgia	5	11	p<0.001
Pyrexia	15	11	p<0.001
Abdominal Pain	35	10.3	p<0.002
Peripheral Edema	0	18.7	p<0.001
Ecchymosis	0	18.7	p<0.001
Insomnia	0	11.6	p<0.001
NGHA: National Guard Health Affairs; AEs: Adverse Events			

Table 4 Reason for dose modification

Reason for Dose modification	n (%)
Thrombocytopenia	1 (5%)
Pancytopenia	2 (10%)
Bleeding	3 (15%)
Pain	4 (20%)
Increase In White Blood Cells	5 (25%)
Fever	6 (30%)
Availability of the Specific Dose	7 (35%)
Anemia	9 (45%)

DISCUSSION

This real-life study demonstrated that treatment with Ruxolitinib inpatient diagnosed with Myelofibrosis appeared to have a significant effect in reducing the symptoms as indicated in the previous trials and to some point reducing spleen size.

This study demonstrated that the decrease in the spleen size seen in patients who received Ruxolitinib was lower than expected, only 20% of the study participant achieved 20%-30% reduction in spleen size and 50% of the patients achieved at least 10% or more reduction in spleen size but no one met the determined goal of reduction of greater than 35% or more whereas in UK ROBUST trial 66.7% of the patients achieved ≥ 50% reduction in the spleen size [15]. COMFORT-I [6] and COMFORT-II trials [16] found that 28% and 45% respectively of the patient achieved at least ≥ 35% reduction in the spleen size from baseline this variation in our finding may be attributable to the duration of the treatment which was 48 weeks in those trials versus 24 weeks in our study [6,16]

Symptoms improvement rate observed in our study are consistent with COMFORT-II [16], UK ROBUST [15], Davis, et al. [14] and Cervantes, et al. [17]. In general symptoms, the improvement rate was higher in our study compared COMFORT-I [6] study except in early satiety and night sweating which showed a similar rate. Most of the study participants showed improvement in symptoms, including those who experienced a minimal reduction in spleen size. Around half of the affected patients showed significant improvement in Fatigue and Bone pain whereas one-third of the patients experienced a decrease in abdominal distress, early satiety and night sweat. Weight loss showed improvement in 15% of the patients.

Our safety findings are generally consistent with the previously published studies, Ruxolitinib considered has an acceptable tolerability profile as shown in previously published studies [14,15]. In our study, Ruxolitinib had a lower side effect rate compared to COMFORT-I trial [6] except for fatigue, abdominal pain, and pyrexia which were higher. Despite the mean reduction in the platelet count reach 26% there were only 1 patient need dose modification unlike the results from COMFORT-I [6], COMFORT-II [16], ROBUST [15] trials and Davis, et al. [14], which revealed a higher rate of thrombocytopenia. The most common reasons for dose modification were anemia and fever followed by an increase in the white blood cells and pain. Least cause for dose modification was bleeding and pancytopenia which is consistent with other studies findings, also we have two patients discontinued the treatment due to anemia versus one patient due to thrombocytopenia.

Our study has a number of limitations. Firstly, it's a retrospective study with a very small sample size. Also, the comparison made with historical controls carries the typical limitations of potential differences in measuring the endpoint and/or missing data. Furthermore, the Symptoms evaluation conducted without using validated scales. There was no classification for study participants based on Myelofibrosis severity. A future large randomized clinical trials from real life need to be conducted with sufficient sample size.

CONCLUSION

Our study demonstrated that Ruxolitinib has clinical benefits for Myelofibrosis patients. It provides a significant improvement in Myelofibrosis related symptoms and it was associated with a reduction in spleen size. Ruxolitinib was considered tolerable and most of the adverse events were controlled by dose modification.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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