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# POLYCYTHEMIA VERA: PRESENTATION AND MANAGEMENT

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**Abstract:**

***Background:*** *Polycythemia vera (PV), alongside primary myelofibrosis (MF) and essential thrombocythemia (ET), is a classic Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) characterized primarily by an expanded red platelet mass. Patients with PV have excessive proliferation of erythroid as well as myeloid and megakaryocytic components in the bone marrow, which result in high red blood cell, white blood cell (WBC), and platelet counts. Clinically, patients with PV may encounter manifestations, for example, pruritus, fatigue, night sweats, bone pain, thrombosis, and bleeding*

***Methodology:*** *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: polycythemia Vera, presentation, complication, diagnosis, and management of Polycythemia Vera, JAK2 mutation, targeted therapy*

***Aim:*** *In this review, we aim to study the clinical presentation, complication, diagnosis, and advances in management of polycythemia Vera.* ***Conclusion:*** *The discovery of JAK2 mutations as the underlying molecular basis for PV has enormously expanded our comprehension of the pathogenesis of PV and has allowed for the development of targeted treatments. As of now, studies are evaluating the clinical advantages of JAK2 inhibitors and are demonstrating promising outcomes for the treatment of this debilitating disease. Further studies will mostly focus around which patients with PV will profit most from the utilization of targeted treatments and how these new treatments compare with present treatment standards. The best treatment for every patient will be one that is well endured while improving symptoms and quality of life, and in such manner, targeted treatments will be valuable tools.*

**Keywords:** *Polycythemia Vera, JAK2 mutation, hematologic pathology*

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## INTRODUCTION:

Polycythemia vera (PV), alongside primary myelofibrosis (MF) and essential thrombocythemia (ET), is a classic Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) characterized primarily by an expanded red platelet mass. Patients with PV have excessive proliferation of erythroid as well as myeloid and megakaryocytic components in the bone marrow, which result in high red blood cell, white blood cell (WBC), and platelet counts. Clinically, patients with PV may encounter manifestations, for example, pruritus, fatigue, night sweats, bone pain, thrombosis, and bleeding. Moreover, patients with PV have a decreased quality of life and are at risk of change to secondary MF and acute myeloid leukemia (AML). Therapeutic options are restricted, and accessible treatments (e.g., low-dose aspirin, phlebotomy, hydroxyurea (HU)) are chiefly palliative and focus on preventing the event of thrombosis and improving symptoms **[1]**.

PV has a lot higher prevalence than does MF (44– 57 for every 100,000 people versus 4– 6 for each 100,000, respectively). In Europe, the frequency of PV ranges around 0.4 per 100,000 people for each year to 2.8 per 100,000 every year, and individuals with PV have a 1.6-fold greater risk of mortality than the general population. PV influences a greater number of men than women, with the median age of diagnosis being around 60 years; nevertheless, roughly around 20 to 25 % of individuals are younger than 40 years. The median survival in individuals with PV is around 14.1 years, yet it is greatly lower in those aging older than 60 years and/or with a past history of thrombotic events (8.3 years) **[2]**.

## METHODOLOGY:

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: polycythemia Vera, presentation, complication, diagnosis, and management of Polycythemia Vera, JAK2 mutation, targeted therapy

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

**Symptoms and Complications**

Symptomatic burden in PV is extreme and present in many patients with the disease. The most well-known complaints are fatigue (reported by 88 % of individuals), pruritus (62 %), night sweats (52 %), bone pain (50 %), fever (18 %), and weight reduction (31 %), with pruritus and fatigue being the most commonly and irritating side effects **[3]**. Pruritus appears as generalized burning, pricking, tangling, or itching and is much of the time presented after water contact (aquagenic pruritus); great temperature shifts, alcohol consumption, or exercise may induce same symptoms. symptoms may be on going for up to 40 min and are often connected with aggression, irritability, depression, and suicidal thoughts. Fatigue has been distinguished as the outcome of circulating cytokines (tumor necrosis factor alpha, interleukin-1, interleukin-6). Moreover, roughly 35 to 45 % of patients may develop splenomegaly, despite the fact that its presence is normally demonstrative of advanced disease. Splenomegaly for the most part results in secondary symptoms, including abdominal pain, early satiety, weight reduction, and nausea, and complications can prompt abdominal organ compression and portal hypertension **[4]**.

PV-related constitutional symptoms and side effects related with splenomegaly are present in 70 % of patients and compromise quality of life, as evaluated by tools, for example, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 as well as the MPN-Symptom Assessment Form (SAF) questionnaires. A condensed version of the MPN-SAF, the MPN-SAF Total Symptom Score, was lately developed to give a productive tool to asses symptom burden in patients with MPN. The MPN-SAF Total Symptom Score is a ten-item scoring instrument concentrating on fatigue, focus, early satiety, inactivity, night sweats, tingling, bone pain, abdominal discomfort, weight reduction, and fevers. In light of these tools, the symptom burden in patients with PV at diagnosis has been observed to be practically identical to or worse than that found in patients with recently diagnosed primary MF **[5]**.

The most common complications of PV are vascular and thromboembolic events and hemorrhages. Thrombosis is a noticeable symptom seen in up to 39 % of patients with PV at diagnosis. The most

continuous types of major thrombosis incorporate stroke, transient ischemic attack, myocardial infarction, peripheral arterial thrombosis, deep venous thrombosis, portal vein thrombosis, and thrombosis of the hepatic veins causing Budd-Chiari syndrome. Besides macrovascular complications, patients may encounter microvascular manifestations (e.g., headaches, dizziness, visual disturbances, distal paresthesia, acrocyanosis), with erythromelalgia being the most characteristic disturbance and comprising of congestion, redness, and burning pain in the extremities. In instances of extreme thrombocytosis (e.g., >1500 × 109/L), patients might be at risk for developing acquired von Willebrand syndrome, which causes a bleeding diathesis. hemorrhage is additionally a significant reason for morbidity and mortality in patients with PV, with a total rate of 39.6 % (6.2 % per individual year). Also, overall survival has been observed to be fundamentally shorter among patients with hemorrhage than among those without this side effect (median overall survival, 94.8 months versus not reached; P = 0.002) **[6]**.

PV additionally carries a risk of transforming into acute leukemia. The occurrence of transformation to AML/myelodysplastic syndrome in patients with PV ranges from 5 to 15 % following 10 years of disease, with progressive risk after some time. Advanced age; female sex; and the use of alkylating medications, radiation, or a combination of cytoreductive medications are related with a higher risk of transforming to leukemia **[7]**.

**Diagnosis**

Diagnosis of PV is made utilizing WHO criteria, and depends on a composite evaluation of clinical and laboratory features, including JAK2 mutation status and serum erythropoietin (Epo) level. The presence of a JAK2 mutation and a subnormal serum Epo level affirms the diagnosis of PV.20A subnormal serum Epo level without JAK2 V617F requires extra mutational investigation for JAK2 exon 12 mutation to distinguish the uncommon patients with PV who are JAK2 V617F negative. Bone marrow examination is not essential for a diagnosis; nevertheless, patients who fulfill the diagnostic criteria for PV may show considerable bone marrow fibrosis **[8]**.

**Management**

treatment options in PV are restricted and no cure is accessible. The objective of current treatments is to prevent the event of thrombosis/vascular events and delay transforming to MF or AML. To this end, treatments for PV focus at targeting a Hct <45 %, as this has been related with a decrease in cardiovascular deaths and thrombotic occasions. Inadequately controlled Hct has been reported to prompt an elevated risk of thrombosis since increased Hct can increase blood thickness, decrease blood return through the venous system, and increase platelet adhesion. A small retrospective landmark trial in PV discovered that the rate of thrombotic expanded linearly in people when Hct was >45 % (range, 46– 52 %). More lately, Marchioli et al. evaluated this suggestion in the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) trial (N = 365), a large-scale, prospective, randomized clinical study looking at the advantages and risks of conventional therapy targeted at maintaining Hct <45 versus 45 to 50 % and discovered a lower rate of cardiovascular mortality and major thrombotic occasions in individuals with a target Hct of <45 % than in patients with a target Hct of 45 to 50 %. The incidence of occasions was 1.1 every 100 patient-years in the low-Hct group in contrast to 4.4 per 100 individual-years in the high-Hct group **[9; 10]**.

Initial therapy relies upon the risk stratification of the patient, which is molded by his or her risk of thrombosis and is not intended to evaluate survival or the risk of leukemic/fibrotic transformation. Patients can be stratified in "high-risk" or "low-risk" categories as per whether they are older or younger than 60 years and known history with thrombosis. Low-risk patients have zero risk factors; high-risk patients have a couple of risk factors. An "intermediate-risk" classification that incorporates younger patients with coexisting cardiovascular risk factors without past history of thrombosis has been proposed yet has not been formally assessed. Leukocytosis and JAK2V617F allele burden have been recognized as novel thrombotic risk factors however have not been affirmed as such yet. In support of leukocytosis being a risk factor, leukocytosis at PV diagnosis has been related with patients having a higher risk of developing artrial thrombosis and acute leukemia, with both of these complications having an outcome of shorter survival **[11]**. Moreover, leukocytosis was observed to be an independent risk factor in the European Collaboration

on Low-Dose Aspirin in Polycythemia (ECLAP) study, and besides, persistence of leukocytosis in spite of therapy with HU was related with a higher risk of hematologic change and shorter survival. unlike leukocytosis, the impact of JAK2 V617F on thrombotic risk is not clear as of date. Studies have demonstrated that patients harboring a >75 % JAK2 V617F allele burden are at higher relative risk of developing major cardiovascular and thrombotic occasions. Nevertheless, a study found no connection among major cardiovascular occasions and JAK2 V617F allele burden. In addition, age >65 years, male sex, and leukocytosis >10 × 109/L at diagnosis are altogether connected with a significantly lesser survival. interestingly, when the different items included into the composite European LeukemiaNet (ELN) response definition were separately considered, being in continued response as related with PV-related symptoms, spleen size by palpation, Hct, or WBC count was not related with any great decrease in the incidence rate of vascular events **[12]**.

Low-risk patients (aging less than 60 years and with no earlier history of thrombosis) are given treatment with low-dose aspirin and phlebotomy. The viability and safety of low-dose aspirin (100 mg daily) were evaluated in the ECLAP double-blind, placebo-controlled, randomized clinical study (N = 518). A follow-up of 3 years demonstrated a huge decrease in cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and major venous thromboembolism; major bleeding was not essentially expanded. Low-dose aspirin can be administered alone (generally in patients with early-period PV) or can be utilized in combination with phlebotomy. Phlebotomy lowers Hct values, in this way decreasing blood hyper viscosity, and ought to be kept until Hct reaches <45 %. Cytoreductive treatment should also be considered for low-risk patients who cannot endure phlebotomy, still have extreme disease-related side effects or progressive splenomegaly or have platelet counts >1500 × 109/L or progressive leukocytosis. adding cytoreductive treatment is likewise recommended for patients at high risk for vascular complications **[13]**.

For high-risk individuals, HU or interferon alpha (IFN-α) are the primary line therapy suggestions; nevertheless, IFN-α is not authorized for therapy of PV in most European countries. HU is a cytoreductive medication that diminishes the production of all cell lines made in the bone marrow. HU is valuable in controlling PV-related side effects, splenomegaly, leukocytosis, thrombocytosis, and Hct. nevertheless, HU-treated individuals can eventually become resistant or encounter unacceptable side effects (HU intolerance), consisting skin ulcers, a decrease in blood cells, gastrointestinal problems, oral ulcers, stomatitis, hyperkeratosis, or actinic keratosis. IFN-α has been appeared to have antiproliferative effects at hematopoietic precursor cells, incite cytogenetic remissions, and diminish JAK2 V617F allele burden in individuals with MPNs. regrettably, intolerable side effects, consisting of influenza like side effects, fatigue, and neuropsychiatric symptoms, and autoimmune disorders, for example, thyroiditis, have restricted its utilization in PV. Moreover, delayed assessment of IFN-α has been quite troublesome due to approximately 25 to 40 % of patients with PV treated with IFN in clinical trials stopped treatment within 1 to 2 years because of side effects **[14]**. Other second-line cytoreductive treatment options for patients who encounter resistance or intolerance to HU incorporate busulfan, pipobroman, or 32P. These agents, nevertheless, have been connected to potential leukemogenicity and are generally held for use in old patients (aged ≥70– 80 years) or those with advanced disease, in whom the risk of thrombosis exceeds the risk of AML/myelodysplastic disorders **[15]**.

**Other Treatments**

With the development of a few new treatments, including targeted agents, standardized criteria for the interpretation and correlation of clinical trials became imperative. In 2013, the ELN and the International Working Group-Myeloproliferative Neoplasms Research and Treatment developed a set of response criteria to be utilized in clinical trials of new agents. The proposed criteria include clinical, hematologic, and histologic response appraisals and assess the long-term effects of new and experimental medications. These criteria are essential for evaluating therapeutic results in patients treated with novel agents and for the approval procedure of these agents by regulatory organizations **[16]**.

**JAK2 Inhibitors**

The discovery of JAK2 V617F as the cause of mutation in PV has prompted the development of a few molecularly targeted treatments concentrating on the inhibition of JAK2. The JAK2 inhibitors have exhibited incredible action in individuals with MF. Patients with PV who are resistant to or intolerant of

HU or IFN as well as are encountering intractable pruritus, extreme constitutional symptoms, or severe splenomegaly may profit incredibly from therapy with a JAK inhibitor, rather than conventional treatment **[17]**.

The 1st reported consequences of a JAK2 inhibitor for the therapy of PV were those from the phase 2 trial of lestaurtinib in individuals with PV/ET. Lestaurtinib has been appeared to inhibit proliferation and JAK2/STAT5 signaling in cells from individuals with myeloproliferative disorders (IC50 = 1 nM in vitro) in preclinical trials. The capacity of lestaurtinib 80 mg twice daily to diminish JAK2 V617F allele burden in patients with PV (n = 27) or ET (n = 12) was examined in a phase 2, open-label, multicenter study (NCT00586651). The primary endpoint, a ≥15 % decrease in JAK2 V617F allele burden in 15 % of patients, was not met. Lestaurtinib modestly decreased JAK2 V617F allele burden and diminished spleen size in a subset of patients. Each patient had ≥1 adverse event (AE), mostly gastrointestinal (95 %), 15 patients (38 %) experienced serious AEs, and 23 (59 %) pulled back due to AEs. This study featured the requirement for further studies of JAK2 inhibition in the treatment of PV as well as the development of other JAK2 inhibitors **[18]**.

In 2011, ruxolitinib, a strong JAK1/JAK2 inhibitor, was accepted by the US Food and Drug Administration (FDA) for the therapy of MF and later on by the European Medicines Agency for the therapy of splenomegaly and MF-related manifestations. These endorsements depended on the outcomes from two phase 3 Controlled Myelofibrosis Study with JAK Inhibitor Therapy (COMFORT) studies demonstrating that ruxolitinib was generally very much endured and exhibited quick and durable clinical advantages, and additionally a survival advantage. Given ruxolitinib's great effects and safety profile in MF and its activity as a JAK inhibitor, trials of its effects in individuals with PV have started. In preclinical studies, ruxolitinib repressed erythroid colony formation from cells originated from individuals with PV and additionally growth- factor-independent colony formation, a special characteristic of PV and other MPNs. outcomes of a phase 2, open-label, dose-ranging trial (Incyte; N = 34) proposed that ruxolitinib was very much endured and accomplished quick and durable clinical reactions in patients with PV who were resistant/intolerant to HU. Reaction was evaluated utilizing modified ELN criteria, which incorporated a decrease in Hct to <45 % without phlebotomy, resolution of palpable splenomegaly, normalization of WBC and platelet counts, and decrease in PV-related manifestations. response was accomplished in 97 % of patients by week 24 (median length of exposure, 155 weeks) and was durable, with 85 % maintaining response for 48 weeks. Ruxolitinib improved PV-related side effects, including pruritus, night sweats, and bone pain within a month of treatment initiation. Anemia and thrombocytopenia (primarily grade 1) were the most well-known AEs **[19; 20]**.

Momelotinib (CYT387), another JAK inhibitor currently under assessment, is a JAK1/JAK2 inhibitor that has exhibited clinical enhancement in MF in a phase 1/2 clinical study. Treatment with momelotinib had an outcome of a durable decrease of splenomegaly and the accomplishment of supported red blood cell transfusion independence in a significant number of participants in this trial. In view of these outcomes, a phase 2, open-label, randomized study assessing the safety and viability of momelotinib in patients with PV or ET is at present in progress (NCT01998828). Patients must be intolerant of, resistant to, or reject current accessible treatment for PV. The primary endpoint is a general response rate characterized as the extent of participants who encounter the majority of the following for ≥4 weeks amid the treatment time period: Hct <45 % without phlebotomy, WBC count <10 × 109/L, platelet count ≤400 × 109/L, and resolution of palpable splenomegaly **[19]**.

One other JAK inhibitor still in the beginnings of development is the selective JAK2 inhibitor LY2784544, which has exhibited dose-dependent selectivity for the mutation of JAK2 V617F over wild-type JAK2. LY2784544 was assessed in a phase 1 study (NCT01134120) in 38 individuals with JAK2 V617F-positive MF (n = 31), ET (n = 1), or PV (n = 6). The main objectives were to determine the safety and tolerability of LY2784544 and to characterize a suggested dose for more studies. Of the six patients with PV, three accomplished a clinicohematologic fractional response at a dose of 120 mg for each day. The most much of the time reported medication related AEs over all grades were diarrhea (44 %); nausea (29 %); elevated creatinine

(21 %); anemia, vomiting, and fatigue (9 % each); there was no grade 4 AEs. The authors presumed that the outcomes support ongoing phase 2 testing at a daily dose of 120 mg **[21]**.

Histone deacetylase inhibitors

Another class of targeted treatment being investigated is histone deacetylase (HDAC) inhibitors, which repress proliferation of tumor cells by inducing cell cycle arrest, differentation, as well as apoptosis. Givinostat has specificity for JAK2 V617F-mutated cells and has been tested in a pilot phase 2 trial in individuals with HU-resistant/intolerant JAK2 V617F-positive PV (n = 12) and ET (n = 1). Givinostat was well endured, with no grade 4 toxicities reported overall, 75 % of patients had a decrease in splenomegaly and 54 % had a clinical response following 12 weeks on treatment. Givinostat was later assessed in a multicenter, open-label phase 2 study in patients with PV (n = 44) who demonstrated no reaction when treated with the greatest endured doses of HU. Patients were treated with givinostat (50 or 100 mg/day) in combination with HU at the most extreme endured dose. The combination of givinostat and HU was well endured, and following 12 weeks of treatment, complete or fractional response was seen in 55 and 50 % of patients taking 50 or 100 mg givinostat, respectively. Enhancements in pruritus were also seen (64 and 67 %). Other HDAC inhibitors have not been well endured. Vorinostat was tested in a nonrandomized, open-label phase 2 trial enlisting patients with PV (n = 44) and ET (n = 19). overall, 72 % of patients had a response, however 44 % of patients suspended treatment due to AEs **[22]**.

Pegylated interferon

newer pegylated formulas of IFN (PEG-IFN), which are greatly endured and allow for less frequent intake, have renewed interest for IFN as a therapeutic alternative for individuals with PV, including the individuals who are refractory or resistant to HU. additionally, having a more beneficial toxicity profile than HU and IFN, PEG-IFN therapy has been related with great rates of hematologic and molecular responses that can avert evolution to MF and AML. A 2008 phase 2 study (N = 37) discovered that all individuals administering PEG-IFN had a hematologic response and a decrease in JAK2 V617F allele burden **[14]**. In the same manner, other study (N = 40) exhibited an overall hematologic response rate of 80 %, with a 14 % complete molecular response. nevertheless, PEG-IFN is not advised in patients with thyroid and mental disorders, and information on its counteractive action of thromboembolic occurrence are limited. PEG-IFN is being assessed in two phase 3 studies for the therapy of PV. The 1st trial, supported by the Myeloproliferative Disorder Research Consortium, is a randomized open-label trial assessing the safety, tolerability, and adequacy of PEG-IFN-2a (Pegasys) versus HU in individuals with high-risk PV or ET (NCT01259856). The primary result will be a correlation of hematologic rates between the two study arms. Pegylated Interferon Alpha-2b Versus Hydroxyurea in Polycythemia Vera (PROUD-PV; NCT01949805), a second phase 3 study, is as of now assessing AOP2014, a novel PEG-IFN, in patients with PV. This study will compare the safety and adequacy of AOP2014 with HU in patients who either have not had earlier presentation to HU or have had no response to earlier HU treatment. The primary endpoint is the disease reaction rate (Hct < 45 % without phlebotomy, platelets <400 g/L, leukocytes <10 g/L, and typical spleen size) at a year. This study is presently recruiting individuals, with an expected enlistment of 256 patients **[23]**.

Management of pruritus

Pruritus, at times aquagenic, is a standout amongst the most irritating, however not really life-threatening complications of PV. In fact, in an ongoing large worldwide study of 1545 patients with PV, presence of pruritus was independently connected with longer survival. Among 441 German patients with PV, 301 (68%) reported pruritus (serious and unbearable in 15%), happening in the majority before the diagnosis of PV. In our very own experience including 418 patients seen at the Mayo Clinic, pruritus at diagnosis was recorded in 31% and was related with a lower rate of blood vessel thrombosis and higher JAK2V617F allele burden. The last observation was affirmed by others as well. Treatment options for PV-related pruritus include antihistamines, selective serotonin reuptake inhibitors (SSRIs), danazol66, IFN-α, narrow band ultraviolet B phototherapy, photochemotherapy with psoralen and ultraviolet A light (PUVA), and JAK2 or mTOR inhibitors. Among these, we suggest beginning treatment with antihistamines and SSRIs, followed by IFN-α treatment for progressively severe and refractory cases, and reserve treatment with JAK2 inhibitors for

high-risk patients with IFN-α-resistant pruritus **[24]**.

## CONCLUSION:

PV is the most well-known of the MPNs. Patients encounter debilitating pruritus, fatigue and the development of new side effects, for example, splenomegaly, as the disease advances, while confronting the risk of major thrombotic events. In spite of the fact that PV is related with increased mortality, numerous patients have a long median survival, featuring the significance of effective and well-endured treatment. Individuals have limited therapeutic options, and a lot of them must seek after insufficient treatment accompanied by intolerable side effects and the risk of complication to MF or hematologic transformation. The new discovery of JAK2 mutations as the underlying molecular basis for PV has enormously expanded our comprehension of the pathogenesis of PV and has allowed for the development of targeted treatments. As of now, studies are evaluating the clinical advantages of JAK2 inhibitors and are demonstrating promising outcomes for the treatment of this debilitating disease. Further studies will mostly focus around which patients with PV will profit most from the utilization of targeted treatments and how these new treatments compare with present treatment standards. The best treatment for every patient will be one that is well endured while improving symptoms and quality of life, and in such manner, targeted treatments will be valuable tools.

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