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ORIGINAL ARTICLE

Differences between aquagenic and non-aquagenic pruritus in myeloproliferative neoplasms: An observational study of 500 patients

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Abstract

Background: Pruritus is a frequent symptom experienced by patients with myeloproliferative neoplasms (MPN). Aquagenic pruritus (AP) is the most common type. The Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) self-report questionnaires were distributed to MPN patients before consultations.

Objectives: The aim of this study was to assess clinical incidence (phenotypical evolution and response to treatment) of pruritus, especially AP, in MPN patients during their follow-ups.

Patients and Methods: We collected 1444 questionnaires from 504 patients [54.4% essential thrombocythaemia (ET) patients, 37.7% polycythaemia vera (PV) patients, and 7.9% primary myelofibrosis (PMF) patients].

Results: Pruritus was reported by 49.8% of the patients, including 44.6% of AP patients, regardless of type of MPN or driver mutations. Patients suffering from pruritus were more symptomatic and had a higher rate of evolution into myelofibrosis/acute myeloid leukaemia (19.5% vs. 9.1%, OR = 2.42 [1.39; 4.32], $p = 0.0009$) than MPN patients without pruritus. Patients with AP had the highest pruritus intensity values ($p = 0.008$) and a higher rate of evolution (25.9% vs. 14.4%, $p = 0.025$, OR = 2.07) than patients with non-AP. Disappearance of pruritus was observed in only 16.7% of AP cases, compared to 31.7% of cases with other types of pruritus ($p < 0.0001$). Ruxolitinib and hydroxyurea were the most effective drugs to reduce AP intensity.

Conclusions: In this study, we demonstrate the global incidence of pruritus across all MPN. Pruritus, especially AP, which is a major constitutional symptom observed in MPN, should be assessed in all MPN patients due to higher symptom burden and higher risk of evolution.

INTRODUCTION

Myeloproliferative neoplasms (MPN) are chronic disorders of myeloid lineages. The three classical MPN are polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF). MPN are clonal disorders due to the acquisition of driver mutations, *JAK2*, calreticulin (*CALR*) and *MPL*, that affect proliferation signalling pathways. Proportion and repartition are different between MPN, but *JAK2*V617F is the most frequent mutation. These neoplasms expose patients to high risk of complications such as thrombosis, haemorrhage and phenotypical evolution [secondary myelofibrosis (MF), accelerated phase (AcPh) or acute myeloid leukaemia (AML)]. The risk of evolution depends on the MPN subtype

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and mutations.[1,2] According to current recommendations, the therapeutic objective of using cytoreductive and antithrombotic drugs is mainly to reduce the thrombotic risk.[3]

Despite the effectiveness of these drugs, alterations of quality of life (QoL) in MPN patients are significant, and new tools have been developed to measure them. For instance, Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) self-report questionnaires are commonly used.[4,5] Studies have highlighted a variety of symptoms (e.g. abdominal, neurological or constitutional symptoms and fatigue) experienced by these patients and the impact on their QoL. The MPN-SAF scoring system rates symptom intensity from 0 to 10. Expression of these symptoms depends on MPN type (patients with PMF have the highest scores), driver mutation (*JAK2*-positive patients have the highest scores), age (older patients have the highest scores) and use of a cytoreductive drug (ruxolitinib acts on MPN symptoms).[6–9]

Among these symptoms, pruritus is one of the most frequent.[6] Pruritus is the generic medical term describing an uncomfortable skin sensation that causes the desire or reflex to scratch. Depending on origin, the pathophysiology (when known), treatments and impact on underlying disease can vary widely. In MPN, pruritus is a symptom frequently described by patients, but a specific pruritus is also observed: aquagenic pruritus (AP), an intense itching sensation without any visible skin changes that begins after contact with water at any temperature and can last for an hour or more.[10] AP is the most frequent and most emblematic pruritus observed in MPN, and it directly and indirectly impacts QoL by causing fatigue, sleep disturbances and depression symptoms, thus altering social and emotional life.[11,12] Long thought to be exclusively associated with PV, we have previously shown that AP is also present in 10%–15% of ET and PMF patients, with some different clinical characteristics between the three MPN (PASYMPLE study – NCT03688490).[12] Furthermore, we showed that AP was not restricted to *JAK2*-positive cases (PANAM study – NCT04018209) and, above all, was associated with a high rate of thrombosis and phenotypic evolution in ET patients.[13]

At our institution, MPN patients systematically fill out MPN-SAF TSS self-report questionnaires before their consultations, which helps clinicians to evaluate clinical efficacy of cytoreductive drugs and identify initial signs of phenotypic evolution. In this study, we have collected these questionnaires and focused on pruritus to describe its incidence, association with other symptoms, variation under cytoreductive drugs and correlation with secondary phenotypic evolutions. Furthermore, we analyzed the differences in profile and complications among MPN patients with AP or non-aquagenic pruritus (non-AP).

METHODS

Patient recruitment

In this study, we used the OBENE database (observatoire brestois des néoplasies myéloprolifératives: NCT02897297), an observational database of MPN patients followed at Brest University Hospital. Patients provided informed consent to have their data used for research. Evolutive events were documented after the completion of the first questionnaire. Patients included in the study were recruited at our institution without prior selection.

MPN-SAF TSS self-report questionnaires

The questionnaires were given to patients before their consultations between February 2015 and January 2020. We analyzed the presence or absence of symptoms (fatigue, early satiety, abdominal discomfort, inactivity, concentration problems, sweating, pruritus, bone pain, fever, weight loss) and QoL. Intensity of each item was evaluated using a visual analog scale (VAS) from 0 to 10 (from no experience of the symptom to worst ever experience of the symptom). A global sum from 0 to 100 was calculated for each patient by adding together all of the values.

Pruritus

Pruritus self-declaration was completed without clinician influence. Patients were separated into four groups according to pruritus declaration at the time of the first completion of the questionnaire (at diagnosis or during the follow-up): (1) absence of pruritus, with a VAS score equal to 0 (= No pruritus group); (2) presence of pruritus, with a VAS score between 1 and 10 (= Pruritus group), which was divided into the following two groups; (3) the AP group, with itching induced by water contact, and (4) the non-AP group, with itching not induced or influenced by water contact. Pruritus intensity was characterized as low (1–3), moderate (4–6) or severe (7–10).

Statistical analysis

Statistical analyses (Student's *t*-tests and chi-squared tests) were performed using the R project (version 3.1.2, BiostatGV website, hosted by the Institute for Statistics and Mathematics of Wirtschaftuniversität Wien). Only two-sided p-values <0.05 were considered significant. Multivariate analyses were performed by logistic regression. We selected the candidate covariates from the set of collected variables in such a way that there were <20% of patients with missing data, and 5% of variables had missing values (Medistica, pvalue.io, a graphic user interface for the R statistical analysis software for scientific medical publications, 2020. Available at https://www.pvalue.io.).

RESULTS

Patient characteristics

We identified 504 patients (274 ET – 54.4%, 190 PV – 37.7% and 40 PMF – 7.9%) who completed self-report questionnaires. We collected a total of 1444 questionnaires,

corresponding to 2.9 questionnaires per patient (ranging from two to seven). The median time between first and last questionnaire was 4.1 years. The characteristics of the patients are shown in Table 1. At the time of completion of the first questionnaire, 40.3% of patients (n = 203) had not had any treatment, while 58.8% of patients had been prescribed hydroxyurea.

Descriptions of pruritus

In our population, 49.8% of patients self-declared suffering from pruritus (Table 1). Patients with pruritus tended to be older ($p \leq 0.01$) individuals of either sex. Patients with all types of MPN experienced pruritus, but more PV patients (59%) experienced it compared to ET and PMF patients (45.3% and 37.5% respectively; $p < 0.01$). We observed that pruritus was reported by patients no matter their mutational status (*JAK2*, *CALR* or *MPL*), but it was reported significantly more often by patients with *JAK2* mutations (79.3% vs. 6% for *CALR*+ and 2.8% for *MPL*+, $p = 0.0005$). Pruritus was also reported by 11.9% of patients without any mutation.

We separated patients with pruritus into AP and non-AP groups. Patients with AP were mainly males ($p < 0.01$), while non-AP was mostly reported by female patients. PV patients suffering from pruritus experienced AP in 60.7% of cases, whereas most patients with ET or PMF experienced non-AP (67.7% and 73.3% respectively; $p < 0.0001$). In total, 35.8% of PV patients experienced AP, compared to 14.6% of ET patients and 10% of PMF patients ($p < 0.00001$). Finally, 50% of patients with *JAK2* mutations and pruritus experienced AP, as opposed to 23% of the pruritic non-*JAK2* patients ($p < 0.01$).

Prescription of cytoreductive drugs differed between these two groups ($p < 0.05$), as shown in Table 1. Anagrelide and hydroxyurea were more frequently prescribed in the non-AP group (78.3% vs. 68.5% respectively) while ruxolitinib and pegylated interferon were more frequently prescribed in the AP group (87.5% and 67.9% respectively, $p \leq 0.001$). During the follow-up, 17.4% of patients with AP received ruxolitinib at least once (35.7% when ET cases were excluded). In the non-AP group, we identified different origins of pruritus: dermatological disease in 34% of patients, kidney dysfunction in 10% and liver dysfunction in 5% (no cause could be identified in 51% of patients).

Intensity of pruritus

The intensity of pruritus was evaluated by each patient on a VAS from 0 to 10. We observed a clear predominance of low to moderate values (39.8% at 1 and 2/10). Nonetheless, 25.6% of patients reported a high intensity (≥6; Figure 1a). Patients with non-AP had a lower intensity of itch (from 1 to 3/10) than patients with AP (from 5 to 9/10; $p < 0.01$), with

TABLE 1 Characteristics of the 504 patients with myeloproliferative neoplasms included in this study.

Parameters	Cohort	No pruritus	Pruritus	*p*	AP	Non-AP	*p*
Nb (%)	504	253 (50.2)	251 (49.8)		112 (44.6)	139 (55.4)	
Median age (years)	68.6	66.9	70.6	0.01	65.5	68.3	0.12
Male (*n*/%)	219 (43.5)	106 (48.4)	113 (51.6)	0.53	63 (55.8)	50 (44.2)	0.0015
Female (*n*/%)	285 (56.5)	147 (51.6)	138 (48.4)		49 (35.5)	89 (64.5)	
PV (*n*/%)	190 (37.7)	78 (30.8)	112 (44.7)	0.004	68 (60.7)	44 (31.7)	<0.0001
ET (*n*/%)	274 (54.4)	150 (59.3)	124 (49.4)		40 (35.7)	84 (60.4)	
PMF (*n*/%)	40 (7.9)	25 (9.9)	15 (5.9)		4 (3.6)	11 (79.9)	
JAK2-mutated (*n*/%)	390 (77.4)	191 (75.5)	199 (79.3)	<0.0001	100 (89.3)	99 (71.2)	0.005
non *JAK2*-mutated (*n*/%):	114 (22.6)	62 (24.5)	52 (20.7)	0.34	12 (10.7)	40 (28.8)	0.0005
CALR-mutated (*n*/%)	36 (7.1)	21 (8.3)	15 (6)		3 (2.7)	12 (8.6)	
MPL-mutated (*n*/%)	18 (3.6)	11 (4.3)	7 (2.8)		2 (1.8)	5 (3.6)	
3NEG-mutated (*n*/%)	60 (11.9)	30 (11.9)	30 (11.9)		7 (6.2)	23 (16.6)	
Abstention (*n*/%)	203 (40.3)	121 (47.8)	82 (32.6)	0.014	32 (28.6)	50 (36)	0.001
Hydroxyurea (*n*/%)	177 (35.1)	83 (32.8)	94 (37.4)		39 (34.8)	55 (39.6)	
Pegylated-interferon (*n*/%)	45 (8.9)	17 (6.7)	28 (11.2)		19 (17)	9 (6.5)	
Ruxolitinib (*n*/%)	15 (3)	7 (2.8)	8 (3.2)		7 (6.3)	1 (0.7)	
Anagrelide (*n*/%)	36 (7.1)	13 (5.2)	23 (9.2)		5 (4.5)	18 (12.9)	
Others (*n*/%)	28 (5.6)	12 (4.7)	16 (6.4)		10 (8.8)	6 (4.3)	
Pruritus at diagnosis (*n*/%)			67 (26.7)		28 (25)	39 (28)	0.67
Pruritus during follow-up (*n*/%)			184 (73.3)		84 (75)	100 (72)	

Abbreviations: AP, aquagenic pruritus; CALR, calreticulin; ET, essential thrombocythaemia; JAK, Janus-activated kinase; MPL, myeloproliferative leukaemia virus oncogene homology; Nb, number; PMF, primary myelofibrosis; PV, polycythaemia vera; 3NEG, triple negative.

a median value of 5/10 in AP patients compared to 2/10 in non-AP patients (Figure 1b; $p < 0.0001$). We did not observe any difference depending on MPN subtype (Figure S1).

Evolution of pruritus

We identified 153 patients, 76 without pruritus and 77 with pruritus at diagnosis, with at least three successive completed self-report questionnaires. In the pruritus group, the initial intensity was moderate (median = 5), but it was higher in the AP group than for other patients (median = 5/10 and 3/10 respectively, $p < 0.0001$; Figure 2). We noticed that median pruritus intensity decreased during follow-up, but only for patients with AP (from 5 to 3/10, $p = 0.08$; Figure 2a). Furthermore, we observed that AP patients taking hydroxyurea and ruxolitinib had the lowest median intensity values: 3.8/10 for hydroxyurea and 3.4/10 for ruxolitinib (Figure 3a). According to the VAS values (low, moderate or severe), the same response profile of reducing the AP intensity was observed with these two drugs. Indeed, 42.5% of patients under hydroxyurea and 46.2% of patients under ruxolitinib, reported a low-level intensity of their AP (difference between hydroxurea and ruxolitinib was not significant; Figure 3b).

Furthermore, pruritus disappeared for 24.7% of patients: 16.7% ($n = 6/36$) of those expressing AP compared to 31.7% ($n = 13/41$) of those with other types of pruritus ($p < 0.00001$). AP disappeared in 14.2% and 12.8% of patients taking hydroxyurea and ruxolitinib respectively.

Finally, we observed the appearance of pruritus in 23.7% patients ($n = 18/76$; eight taking hydroxyurea, four taking anagrelide, three taking ruxolitinib and three taking other drugs), with a median pruritus intensity value of 4/10 ($p < 0.0001$; Figure 2). No cases of AP were found among these patients.

Other symptoms reported by MPN-SAF TSS self-report questionnaires

Analysis of other items included in the MPN-SAF TSS questionnaires is shown in Table 2. Median VAS scores not equal to 0 were observed for only four items: inactivity, concentration problems, impact on QoL and fatigue. Among all symptoms, fatigue had the highest reported intensity (median = 4/10). The median total score was 18/100 in the whole population, but 26/100 in the pruritus group as opposed to 13/100 in the no pruritus group ($p \leq 0.001$). Patients with pruritus more frequently reported the presence of all symptoms except for weight loss and fever ($p < 0.0001$). Despite higher median values expressed by AP patients, no significant difference was found between AP and non-AP patients.

Phenotypical evolutions

Among our 504 patients, we observed 72 patients with 77 phenotypical evolutions (14.3% of the cohort): 51 evolutions into secondary MF and 26 into secondary AcPh/AML (Table 3). Among these evolutions, 49 (68% of cases) occurred in the pruritus group, compared to 23 (32%) in the non-pruritus group ($p = 0.0009$, OR = 2.42 [1.39; 4.32]). There were more secondary MF and AcPh/AML evolutions in the first group: 13.9% versus 6.3% ($p < 0.01$, OR = 2.39 [1.25; 4.78]) and 7.2% vs. 3.2% ($p < 0.05$), OR = 2.32 [0.96; 6.4] respectively.

The global number of evolutions was higher in the AP group than in the non-AP group (25.9% vs. 14.4%, $p < 0.05$; OR = 2.07 [1.05; 4.15]). The same was true for secondary MF when compared to the non-AP group (21.4% vs. 7.9%, $p < 0.01$; OR = 3.16 [1.41; 7.53]), but also when compared to patients without pruritus (21.4% vs. 6.3%, $p < 0.001$; OR = 3.64 [1.71; 7.96]).

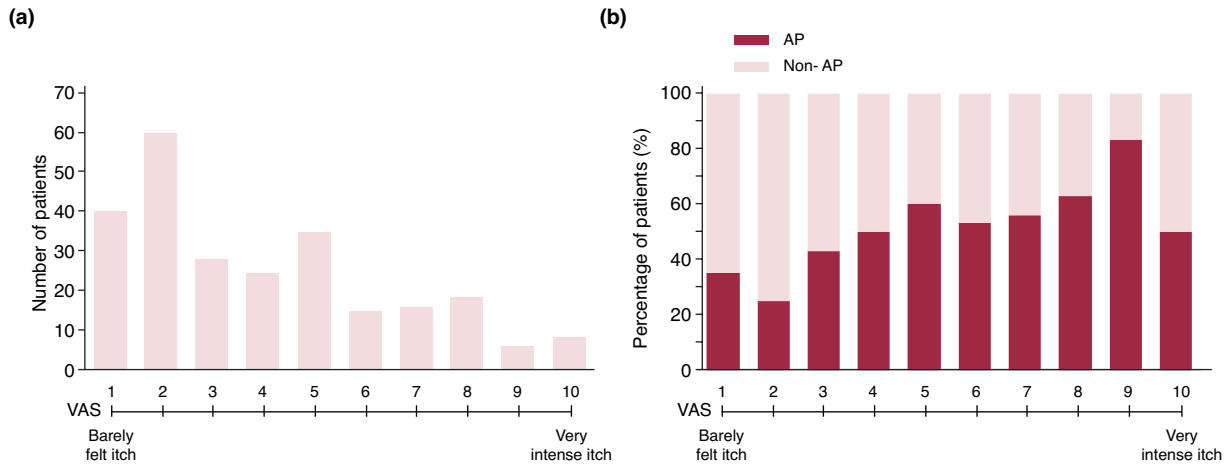

FIGURE 1 Repartition of the subjective intensity of pruritus reported by the 251 myeloproliferative patients with pruritus on visual analogic scale: global population (a), according to AP or non-AP pruritus profile (b). AP, aquagenic pruritus; VAS, visual analogic scale.

Pruritus in the MPN cohort (MPN-SAF TSS)					
At the first completion	**At the last completion**	**Initial intensity of pruritus**	**Final intensity of pruritus**	***p* (fin. vs ini.)**	***p* (fin. vs fin.)**
No pruritus (*n* = 76)	New pruritus (*n* = 18, 23.7%)	0	4	<0.00001	<0.00001
	No pruritus (*n* = 58, 76.3%)	0	0	1	
Pruritus (*n* = 77)	Pruritus (*n* = 58, 75.3%)	5	3	0.44	<0.00001
	No more pruritus (*n* = 19, 24.7%)	5	0	<0.00001	
AP (*n* = 36)	AP (*n* = 30, 83.3%)	5	3	0.08	<0.00001
	No more AP (*n* = 6, 16.7%)	5	0	<0.00001	
Non-AP (*n* = 41)	No AP (*n* = 28,68.3%)	3	3	0.61	<0.00001
	No more pruritus (*n* = 13, 31.7%)	3	0	<0.00001	

FIGURE 2 Evolution of pruritus during the study. AP, aquagenic pruritus; fin, final; ini, initial.

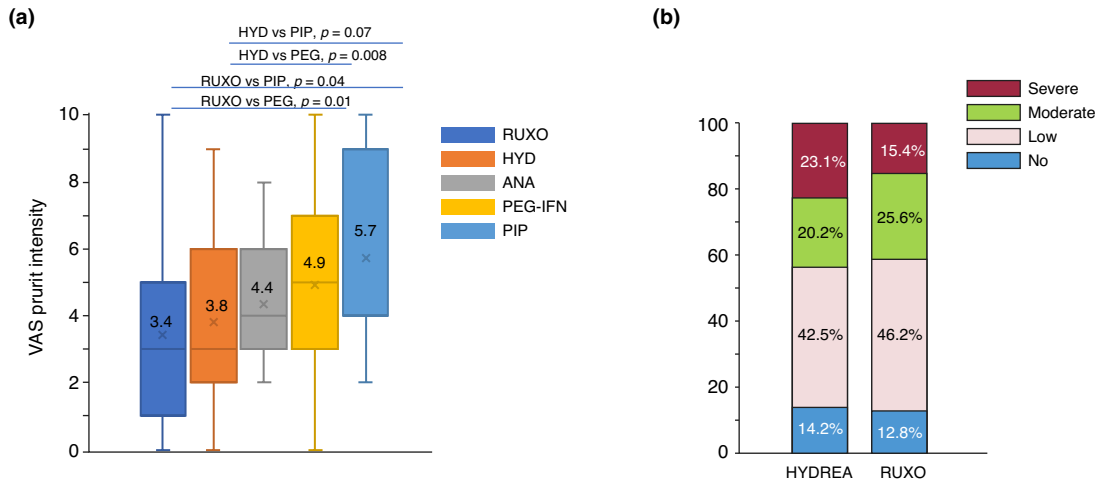

FIGURE 3 Effect of cytoreductive drugs on aquagenic pruritus intensity. (a) Numbers in the box represented median value of itch intensity. (b) Repartition at the end of the study of patients treated by hydroxyurea or ruxolitinib according to the AP intensity evaluated on VAS. Data are expressed in percentage. No: VAS = 0; low: VAS = 1-2-3; moderate: VAS = 4-5-6; Severe: VAS = 7-8-9-10. ANA, anagrelide; HYD, hydroxyurea; PEG, pegylated-interferon α2a; RUXO, ruxolitinib; PIP, pipobroman.

According to multivariate analysis (age, mutations, treatments, non-AP, AP), AP was the sole significant risk factor predictive of evolution (OR = 2.16 [1.24; 3.74], $p < 0.01$), despite a higher number of patients in the hydroxyurea group ($n = 31$) compared to patients taking pegylated interferon and ruxolitinib (14 and 11 respectively; not significant). When we analyzed the ET group, only the *JAK2*V617F mutation was associated in addition to AP with evolution (not *CALR* or triple-negative status, $p < 0.01$, OR = 4.38 [1.88; 10.3], data not shown), but AP was found to be a risk factor of evolution in all groups ($p < 0.001$).

DISCUSSION

Aquagenic pruritus is such a prominent symptom in PV patients that dermatology experts recommend testing patients with AP for *JAK2* mutations to identify MPN cases (mostly in the presence of abnormal blood counts, but not exclusively), as AP can precede MPN diagnosis by many years.[14–16] However, AP is not seen exclusively in MPN and may be present in many other situations.[14,17]

In the present study, we analyzed the frequency, intensity and clinical relevance of pruritus among MPN patients by using MPN-SAF TSS self-report questionnaires. Furthermore, we also distinguished patients with AP from patients with other types of pruritus. We analyzed 1444 questionnaires from 504 patients with ET, PV or PMF. The self-report questionnaires were distributed before consultations and completed by the patients themselves, without the influence of practitioners.

Overall, 49.8% of MPN patients expressed pruritus when completing the first questionnaire. Pruritus was more frequently described by patients suffering from PV (59% of the total MPN population of our study), with AP slightly predominant in these patients (51.9% of PV patients with pruritus and 35.8% of all PV patients). In previous publications, the incidence of pruritus has been reported between 31% and 71.8%, but many of these publications have not provided information about the type of

TABLE 2 Expression of intensity of symptoms listed in the MPN-SAF self-report questionnaires. Results are presented from the highest to the lowest odd ratio in each group. Units expressed in number/percent.

	With pruritus			Without pruritus			*p*	
Symptoms	**No exp**	**Exp**	**Intensity**	**No exp**	**Exp**	**Intensity**	**wP vs. w/o P**	**OR**
Abdominal incomfort	93 (37.1)	158 (62.9)	2	175 (69.2)	78 (30.8)	0	<0.00001	3.8 [2.59; 5.61]
Sweats	111 (44.2)	140 (55.8)	1	183 (72.3)	70 (27.7)	0	<0.00001	3.29 [2.24; 4.87]
Fatigue	25 (10)	226 (90)	4	58 (22.9)	195 (77.1)	3	0.0001	2,68 [1.58; 4.66]
Concentration problem	88 (35.1)	163 (64.9)	2	149 (58.9)	104 (41.1)	0	<0.00001	2.65 [1.82; 3.87]
Bone pain	132 (52.6)	119 (47.4)	0	182 (71.9)	71 (28.1)	0	<0.00001	2.31 [1.57; 3.40]
Early satiety	103 (41)	148 (59)	1	155 (61.3)	98 (38.7)	0	<0.00001	2.27 [1.57; 3.30]
Inactivity	85 (33.9)	166 (66.1)	3	130 (51.4)	123 (48.6)	0	0.00007	2.06 [1.42; 3]
Fever	244 (97.2)	7 (2.8)	0	253 (100)	0	0	0.007	INF
Weight loss	229 (91.2)	22 (8.8)	0	223 (88.1)	30 (11.9)	0	0.3	0.71 [1,28; 0.40]
	AP			**No AP**			*p*	
Symptoms	**No exp**	**Exp**	**Intensity**	**No exp**	**Exp**	**Intensity**	**AP vs. no-AP**	**OR**
Fatigue	8 (7.1)	104 (92.9)	5	17 (12.2)	122 (87.8)	4	0.21	1.81 [4.37; 0.75]
Abdominal incomfort	36 (32.1)	76 (67.9)	2	57 (41)	82 (59)	1	0.19	1.47 [2.47; 0.87]
Inactivity	33 (29.5)	79 (70.5)	3	52 (37.4)	87 (62.6)	2	0.23	1.43 [2.44; 0.84]
Weight loss	101 (90.2)	11 (9.8)	0	128 (92.1)	11 (7.9)	0	0.66	1.27 [3.04; 0.53]
Concentration problem	36 (32.1)	76 (67.9)	2	52 (37.4)	87 (62.6)	2	0.43	1.26 [2.13; 0.75]
Early satiety	46 (41.1)	66 (58.9)	1,5	57 (41)	82 (59)	1	1	0.997 [1.65; 0.60]
Bone pain	60 (53.6)	52 (46.4)	0	72 (51.8)	67 (48.2)	0	0.8	0.93 [1.53; 0.57]
Fever	109 (97.3)	3 (2.7)	0	135 (97.1)	4 (2.9)	0	1	0.93 [4.24; 0.20]
Sweats	51 (45.5)	61 (54.5)	1	60 (43.2)	79 (56.8)	1	0.8	0.9 [1.50; 0.55]

Abbreviations: AP, aquagenic pruritus; Exp, expression; OR, odd ratio; P, pruritus.

pruritus experienced.[6–7,10,18,19] When the type was specified, the proportion of AP cases varied widely between 41.2% and 68.3%.[10,20] In the MPN-SAF and MPN-SAF TSS self-report questionnaires, patients are asked about pruritus without specifying the type (AP or non-AP).[4,5] In our study, a physician inquired about the type of pruritus when a patient rated the intensity of their pruritus with a score > 0. Therefore, our study also shows that AP can be expressed by patients with MPN besides PV, including ET (14.6%) and PMF (10%), and regardless of a patient's driver mutation status.[12,13]

The pruritus intensity varied widely depending on the type of pruritus and between patients. A quarter of the patients described an itch intensity higher than or equal to six on the VAS, corresponding to a grade of moderate to severe. Among this group, patients with AP experienced the highest intensity.[10,12] Under treatment, pruritus disappeared in 24.7% of patients in this group, but mostly in those with non-AP (31.7% vs. 16.7%, $p < 0.0001$). The fact that the number of patients describing relief of their pruritus is higher in the non-AP group than in AP group is not so surprising. Indeed, despite a partial or complete haematological response to haematological treatment, more than 50% of patients reported persistent AP, and the high number of case reports describing fluctuating success of symptomatic treatments suggests that cytoreductive treatments are not the solution.[13,16,18] The absence of a real understanding of the pathophysiology of AP could explain this finding. A correlation between the *JAK2*V617F mutation and the presence of AP has been evoked, but the presence of AP in MPN patients negative for *JAK2*V617F indicates that no direct link exists.[13,16,21–23] The non-AP group may have experienced higher levels of pruritus resolution as a result of better therapeutic management due to an understanding of the cause of the pruritus (i.e. liver or kidney disease or dermatosis) and/or use of the MPN cytoreductive treatment. In the AP group, we observed that more MPN patients described relief of their AP when they received ruxolitinib or hydroxyurea, suggesting that these drugs give better results than the others drugs in controlling AP. However, it is also important to note that the complete relief of AP was only observed in rare cases under these drugs; instead, we mainly observed a diminution of the median values of pruritus intensity. Furthermore, these intensity values remained over three, which could still induce a chronic alteration of QoL. There are two therapeutic possibilities that might improve the clinical status of MPN patients: change the cytoreductive drug used or add a symptomatic drug. Among haematological drugs, ruxolitinib is frequently associated with improvement of clinical symptoms associated with MPN,

TABLE 3 Phenotypical evolutions observed in the cohort.

	Global population		Pruritus		no pruritus		*p*	
Evolutions	**Evol**	**No evol**	**Evol**	**No evol**	**Evol**	**No evol**	**P vs. no P**	**OR**
Nb	504		251		253			
Any (*n*/%)	72 (14.3)	432 (85.7)	49 (19.5)	202 (80.5)	23 (9.1)	230 (90.9)	0.0009	2.42 [1.39; 4.32]
MF (*n*/%)	51 (10.1)	453 (89.9)	35 (13.9)	216 (86.1)	16 (6.3)	237 (93.7)	0.0049	2.39 [1.25; 4.78]
AcPh/AML (*n*/%)	26 (5.2)	478 (94.8)	18 (7.2)	233 (92.8)	8 (3.2)	245 (96.8)	0.046	2.32 [0.96; 6.4]
	AP		**no AP**		**AP vs. no AP**		***p***	
Evolutions	**Evol**	**No evol**	**Evol**	**No evol**		**OR**	**AP vs. no P**	**OR**
Nb	112		139					
Any (*n*/%)	29 (25.9)	83 (74.1)	20 (14.4)	119 (85.6)	0.025	2.07 [1.05; 4.15]	0.0007	2.59 [1.45; 4.62]
MF (*n*/%)	24 (21.4)	88 (78.6)	11 (7.9)	128 (92.1)	0.003	3.16 [1.41; 7.53]	0.0004	3.64 [1.71; 7.96]
AcPh/AML (*n*/%)	8 (7.1)	104 (92.9)	10 (7.2)	129 (92.8)	1	0.99 [0.33; 2.9]	0.1	2.35 [0.75; 7.4]

Abbreviations: AcPh, accelerated phase; AML, acute myeloid leukaemia; AP, aquagenic pruritus; Evol, evolution; MF, myelofibrosis; Nb, number; OR, odd ratio; P, pruritus.

particularly pruritus.[9,24,25] However, switching the existing cytoreductive drug to ruxolitinib for persistence of clinical symptoms in patients despite complete haematological responses has never been tested in trials. Ruxolitinib is an approved *JAK2*-inhibitor for both PV and MF patients (but not for ET patients). Its price should restrict its use to patients with resistance to alternative therapeutics. Furthermore, its potential risk for second neoplasms and immunodepression should also be considered.[26–28] In our cohort, 17.4% of the patients with MPN received ruxolitinib, 35.7% when ET cases were excluded, and the relief of pruritus under this treatment remains quite rare. Despite the small number of patients in each treatment group, this paper is the first to analyze the impact of all cytoreductive drugs on AP.

When a cytoreductive drug is not able to relieve AP, symptomatic drugs could be considered. However, many have already been tested to improve AP, including anti-histamines, anti-depressants, and corticosteroids, and none of them has clearly emerged as an efficient solution.[9,29] In 2013, an international consensus of dermatologists identified hydroxyzine (anxiolytic) as the first-choice drug to improve AP without resolving it. However, the improvement observed in AP was assimilated by this group of experts to a placebo effect.[30] In order to find an efficient therapeutic alternative to treat AP in MPN, we are conducting a prospective trial comparing hydroxyzine to aprepitant in patients with severe AP resistant to cytoreductive drugs (acronym: APHYPAP, NCT03808805).[31] Aprepitant is an anti-NK-1R substance P receptor that has been identified as active on dermatological and lymphoid-related pruritus.[32]

Furthermore, we also retrospectively studied patient outcomes and found that our patients with pruritus had a higher risk of phenotypical evolution (secondary MF or AcPh/AML). Indeed, 68% of these evolutions were seen in the pruritus group (19.5% vs. 9.1%, $p < 0.001$, OR = 2.42). This situation was particularly true for secondary MF ($p < 0.01$, OR = 2.39). A similar trend was apparent when comparing patients with AP to those without. On the other hand, no difference was seen in terms of MPN subtypes or mutation except for the risk of evolution to AcPh/AML in ET patients suffering from AP for whom the risk of evolution was increased when they were *JAK2*V617F positive ($p < 0.01$, OR = 4.38). This is the first report making a real distinction between AP and non-AP in MPN patients and its consequence on disease. The correlation we found between AP and adverse evolution suggests a possible pathophysiological link (OR = 2.16, $p < 0.01$). In a previous report, Tefferi et al. indicated that pruritus was associated with higher survival rates.[33] Our results do not contradict the previous study, because we did not study survival, but instead phenotypical evolution. In 2019, we demonstrated the same phenomenon with ET patients suffering from AP, who presented a lower death rate despite an excess of thrombotic events.[13] In the present study, we clearly distinguished AP from non-AP, a distinction that has not previously been made. Contrary to AP, we did not find a negative impact of non-AP on MPN. One explanation could be the presence of specific cytokines associated with inflammation that can be observed in both patients with pruritus and patients with haematological evolutions. Indeed, MPN are chronic conditions that carry an inflammatory profile, including high levels of C reactive protein (CRP) and inflammatory cytokines (IL-6, IL-8, GM-CSF, HGF, VEGF, b-FGF, TNF-α and TGF-β). This inflammatory profile is frequently associated with pruritus in general, as well as with a higher symptom burden and higher risk of evolution among MPN patients.[34–36] Different patterns of cytokines between MPN may be related to the different mutations observed in these diseases.[37] However, with the exceptions of Gangemi's study in 2012 showing no correlation between IL-10, Il-22 and Il-23 expression and the presence of AP in PV patients and Ishii's 2009 study evoking

the role of IL-31, there has been no systematic study exploring the cytokine profile of MPN patients in relation to the presence or absence of pruritus.[38,39] To assess the impact of cytokines in these situations, we are waiting for the results of the APHYPAP prospective trial, in which cytokines will be explored deeply.[31] A non-mutually exclusive explanation for the difference between AP and non-AP groups could be the presence of additional mutations that might be associated with pruritus and a higher risk of evolution. The classic mutations carried by MPN patients can also acquire additional mutations that can modify the initial mutation and the evolutive profile of the patients. These additional mutations commonly affect genes involved in DNA methylation, histone modification, mRNA splicing, signalling pathways or transcription factors.[40]

In this study we have presented important data concerning the impact of the presence of pruritus, especially AP, in MPN patients. In conducting a retrospective study, we have striven to apply accurate methodology during its duration. Nonetheless, it was performed in only one centre (which specializes in MPN), and such studies should be performed in other centres to confirm or disprove our findings. One could argue that some results could have be influenced by physicians, but with four different physicians involved in this study, we would suggest that this concern is unfounded. Furthermore, questionnaires were completed by patients before their consultations. This timing could explain why some patients struggled to correctly evaluate the intensity of their symptoms. No modification of evaluations was done during or after patients' completion of the questionnaire. In total, 90% of the questionnaires distributed were completed. The 10% not completed were attributed to elderly patients who were unable to complete the evaluations, along with the questionnaire not being available during a four-month period. On the other hand, 100% of pruritus information was collected, as physicians systematically asked about it during consultations. The follow-up time of 4.1 years could be considered short, but the numbers of patients and the medical events that occurred allowed us to arrive at sound conclusions. Although, the study was funded by a pharmaceutical laboratory, analyses and results were not checked or controlled by the funder before submission. We had complete independence in our research, even though we highlighted some drugs as more effective than others at reducing AP intensity.

CONCLUSION

In this retrospective study, we analyzed a vast number of MPN-SAF TSS self-report questionnaires completed by MPN patients. We clearly showed the importance of identifying patients with pruritus, who are more symptomatic and at the highest risk of phenotypic evolutions. Furthermore, we found differences in patients with AP compared to those with non-AP. Patients with AP had more symptomatic profiles and higher risk of evolutions. Therefore, clinicians must go beyond simply determining the presence or absence of pruritus to determine whether patients are experiencing AP.

AUTHOR CONTRIBUTIONS

JCI conceived the study. JCI and CLGI wrote the paper. EL and LM reviewed the paper and the English spelling. ASF performed the statistical analyses. JCI, EL, BPP included patients. LH and LR collected questionnaires. All the authors approved the final version of the article.

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JCI received a grant from Novartis SA. CLGI, ASF, EL, LR, LM, LH and BPP have no disclosure to declare.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATMENT

The patients in this manuscript have given written informed consent to publication of their case details.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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