Omalizumab alleviates pruritus in myeloproliferative neoplasms

Chronic pruritus is common in patients with myeloproliferative neoplasms (MPN), particularly in polycythemia vera (PV). Pruritus is typically of aquagenic character, where an intense pruritus is evoked by skin contact with water, but may also include a stinging, burning, or tingling sensation. In contrast to urticarial disease, aquagenic pruritus is typically not associated with visible skin changes. It is most commonly localized centrally on the body: thorax, abdomen, back and proximal extremities.[1] Pruritus in MPN may also be more generalized and be triggered by other factors than water contact. Pruritus is prevalent in PV, where 31-69% of patients suffer from chronic pruritus, and 15% report aquagenic pruritus of unbearable intensity.[1] Pruritus also occurs in other subtypes of MPN but the prevalence and severity is not as well characterized.[2] Chronic pruritus in MPN may result in a substantially compromised quality of life and lead to anxiety and depressive symptoms, as well as water-avoiding behaviors with negative effects on personal hygiene and social interaction.[3, 4]

Several treatment options have been reported to alleviate MPN-related pruritus, including hydroxyurea, interferons, ruxolitinib, normalization of hematocrit by venesection, antihistamines, SSRI (paroxetine and fluoxetine), narrow-band UV-B light, psoralen UV-A light (PUVA), and alkalization of bathing water.[5] Interferons are described to have better effect against pruritus than hydroxyurea with a reported efficacy of 81%.[6] JAK2 inhibition with ruxolitinib has also been reported to reduce pruritus.[7] Interestingly, SSRI has been shown to alleviate symptoms in eight of ten described patients.[8] Despite numerous alternatives, MPN-related pruritis refractory to current treatments remains a clinical challenge. In addition, pruritus may occur in younger individuals with low risk of thrombosis, where cytoreduction is not otherwise indicated, or in patients with intolerance to available cytoreductive therapies. Therefore, there is a great clinical need to find novel approaches to alleviate refractory MPN-related pruritus.

Omalizumab is a humanized monoclonal immunglobulin E (IgE) antibody, that binds with high affinity to free IgE and prevents receptor binding. Omalizumab is Food and Drug Adminstration-approved for refractory asthma, nasal polyps and chronic idiopathic urticaria. Here we describe a series of patients with MPN that were treated with omalizumab for severe pruritus.

We describe seven patients with intense chronic pruritus related to PV and essential thrombocythemia (ET) treated with omalizumab at the Karolinska University Hospital. The diagnoses of PV and ET were defined according to the World Health Organization 2016 criteria. The data presented were retrieved from medical charts. Complete res-

Table 1. Descriptive characteristics of patient demographics, pruritic character and effect of omalizumab.

Patient	Age in years	Sex	Diagnosis	Driver mutation, VAF%	Current treatment	Hematologic control with current treatment	Previous treatments	Character of pruritus	IgE (kU/L)*	Tryptase (μg/L)#	Effect of omalizumab
1	50	F	ET	*MPL*, na	IFNα, aspirin	Yes	Antihistamines	P	140	na	Complete
2	81	M	ET	*JAK2*, 31	HU, apixaban	Yes	Antihistamines	P	na	na	Partial
3	56	M	PV	*JAK2*, 39	IFNα, aspirin	Yes	Antihistamines, HU	AP	22	3.9	Complete
4	69	M	PV	*JAK2*, 25	HU, warfarin	Yes	Antihistamines	AP	na	na	Partial
5	75	M	PV	*JAK2*, 79	HU, apixaban	No	Antihistamines, HU, IFNα, corticosteroids	AP	11	28	Partial
6	55	F	PV	*JAK2*, 97	HU, aspirin	No	Antihistamines, IFNα	AP	110	2.7	Complete
7	36	M	ET	*JAK2*, na	aspirin	No	IFNα, antihistamines, corticosteroids	AP	230	4.1	Partial

*Reference value <114 kU/L; #reference value <11 μg/L. VAF: variant allele frequency; PV: polycythemia vera; ET: essential thrombocythemia; IgE: immunoglobulin E; F: female; M: male; AP: aquagenic pruritus; P: pruritus; HU: hydroxyurea; IFNα: pegylated interferon-α; na: not available.

olution was defined as patients describing the pruritus as being completely gone, partial resolution as patients describing the pruritus being clearly reduced but not entirely gone.

The MPN subtypes were subtype was PV in four patients and ET in three. The median age of the patients were 56 years (range, 36-81) at time of starting omalizumab, and the duration of pruritus prior to omalizumab treatment ranged from 5 months to several decades (Figure 1; Table 1). Three of the patients were classified as low-risk regarding thrombosis, according to the revised IPSET score in ET and by age above 60 years or previous thrombosis in PV. Six of the patients stated pruritus as their main complaint at the time of initiation of omalizumab. Five of the patients described classic aquagenic pruritus, while two had a more generalized pruritus, not triggered by specific agents or situations. In the patients with aquagenic pruritus, pruritic crisis could also be induced by other triggers such as physical activity, getting dressed, or during sleep. Two of the patients described visible skin changes, both were patients with generalized pruritus. In four of the patients, a dermatologist had been consulted, one of the patients with generalized pruritus had received a diagnosis of chronic urticaria that presented concurrently with the MPN diagnosis, the others did not receive a specific dermatological diagnosis. Previous and current treatments are shown in Table 1. All previous treatments had either an insufficient effect on their pruritus or were stopped due to intolerable side effects. None had tried ruxolitinib, SSRI or UV light therapies. Pretreatment measurement of IgE and tryptase showed normal values in the majority of the patients (Table 1).

Omalizumab was introduced in doses varying between 150 mg to 300 mg every second to fourth week as a subcutaneous injection, at the discretion of the responsible clinician. The first two to three doses were administered at the hematologic day care unit or in a primary care setting. For the subsequent doses self-administration at home was offered as an alternative. Three patients described complete resolution of pruritus after introduction of omalizumab while four patients described partial resolution. In all four patients with partial resolution, a significant improvement was described, and pruritic symptoms were more manageable. For example, patient 4 graded his pruritus, on a numerical rating scale between 0-10 before (0 no pruritus at all, 10 worst possible pruritus) as grade 8 during treatment with hydroxyurea, grade 7 with the addition of high dose antihistamines, and reduced to grade 1 after introduction of omalizumab, increasing to grade 2-3 during the last week before the next injection.

Treatment response was in general observed already after the first cycle of omalizumab, and further improved during the first 3 months. Three patients described a return of

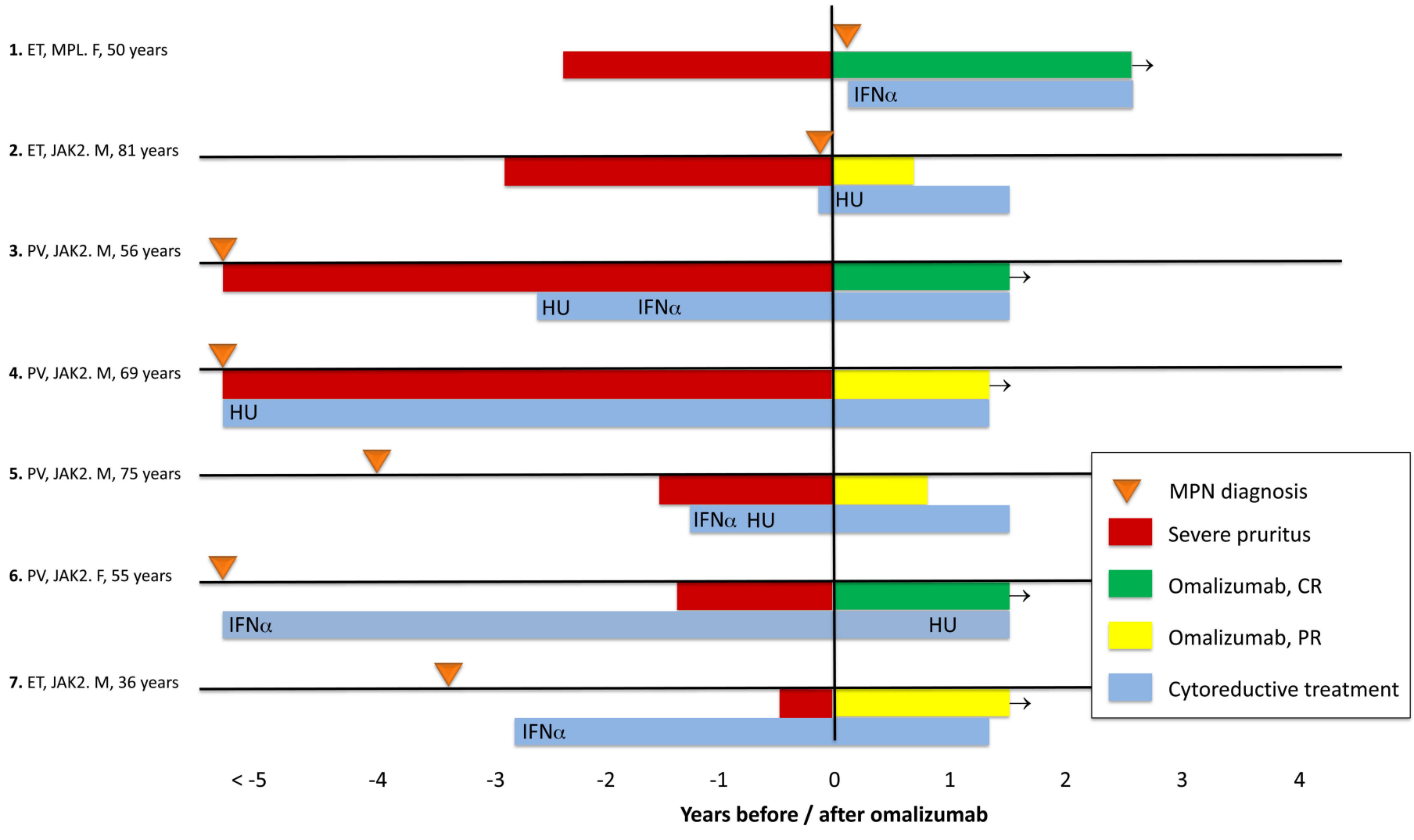

Figure 1. Time of myeloproliferative diagnosis, onset of pruritic symptoms, cytoreduction, omalizumab, and follow-up time. Introduction of omalizumab is set as time point zero. MPN: myeloproliferative; PV: polycythemia vera; ET: essential thrombocythemia; M: male; F: female; HU: hydroxyurea; IFNα: pegylated interferon-α; → : ongoing treatment; CR: complete remission; PR: partial remission.

low-grade pruritus during the last few days before the next scheduled injection of omalizumab, and in one patient this led to shortened dosage interval. One patient with complete resolution of pruritus for an extended period of time was able to taper omalizumab treatment to 300 mg every 10 weeks with a maintained effect (patient 1). The median duration of omalizumab treatment was 13 months (range, 6-31). Three patients are currently still on omalizumab treatment. The four patients who discontinued omalizumab reported doing so due to pruritic symptoms being at a manageable level without omalizumab. No adverse events or side effects related to omalizumab treatment were described by any of the patients. Consent was obtained from all patients to having their cases reported in a scientific journal. The Ethics Review Board was consulted and had no ethical concerns.

The pathophysiology behind pruritus in MPN is not fully understood although basophils and mast cells are considered to play important roles. MPN patients have an increased number of activated basophils that are hypersensitized to IL-3 which can be partially reversed by blocking JAK2.[9] Mast cells are increased in numbers in MPN and are functionally abnormal with increased sensitivity to several pruritic mediators.[10] Omalizumab effectively reduces the level of free IgE in serum, and thus prevents degranulation of mast cells as well as basophils, and thus enables mast cell and eosinophil apoptosis.[11, 12] Off-label usage has been explored in a wide range of diagnoses in allergology, rheumatology, pulmonology and dermatology. Accumulated evidence from other indications demonstrate that omalizumab is medically safe with few observed side effects.[13] There is one case report of successful treatment with omalizumab of idiopathic aquagenic pruritus.[14] A study of chronic urticaria and omalizumab included one patient with concomitant PV where the pruritus responded to omalizumab.[15] To our knowledge, no clinical trial with omalizumab is ongoing in hematological disorders (*clinicaltrials gov. Identifier*: no entry as of October 2022).

There are several limitations to our study, the most important being that this is a retrospective case series and not performed as a study with a preplanned protocol. Further, pruritus was not graded by a validated instrument, for example 5D itch scale or PRURITOOLS. It is conceivable that the pruritus observed in the two patients who had visible skin changes associated was unrelated to their myeloproliferative disease. However, their pruritic symptoms – including chronic urticaria – presented concurrently with the MPN diagnosis.

MPN-related pruritus has a major impact on quality of life and symptom-relief of these patients is an urgent medical need. Our case series suggests that the IgE-blocking monoclonal antibody omalizumab is efficacious in MPN patients with severe refractory pruritic symptoms. The results support an involvement of IgE, basophils and mast cells as important pathogenic factors, however improved understanding of the pathophysiologic mechanisms is warranted to be able to better tailor effective treatment.

Omalizumab is considered safe and has been widely used in other indications since its Food Drug Administration-approval in 2003, and all seven patients in this cohort responded to treatment, with complete resolution in three patients. We therefore propose that omalizumab could be a valuable addition to the treatment arsenal for the management of refractory chronic pruritus in MPN. Prospective validation of these findings is warranted, preferably in a randomized clinical trial, to establish efficacy and optimal dosing regimen.

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All authors took part in clinical treatment and assessment of the patients. ARL and MJ collected the data and wrote the manuscript. All authors critically assessed and approved the final manuscript.

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Data-sharing statement

The authors are not allowed to share data.

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