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LETTER

Inflammatory disorders in IDH-mutated myeloid neoplasms: Characteristics and response to IDH inhibitors

Romain Stammler[1] | Peter Chen[2,^] | Orianne Debeaupuis[2,^] | Lin-Pierre Zhao[3,4] | Mirabelle Ruyer-Thompson[1] | Eve Zakine[1] | Julien Rossignol[5] | Lauriane Goldwirt[6] | Thibault Comont[7,8,9] | Maël Heiblig[10] | Lionel Adès[3,4] | Marie Sebert[3,4] | Jean-Sébastien Allain[11] | Julien Campagne[12] | Marie-Anne Couturier[13] | Marina Cumin[14] | Marie-Caroline Dalmas[15] | Guillaume Denis[16] | Cécile Devloo[17] | Adrien De Voeght[18] | Louis Drevon[19] | Pierre Duffau[20] | Sophie Georgin-Lavialle[21] | Delphine Gobert[1] | Olivier Kosmider[22] | Frédéric Rieux-Laucat[2] | Noémie Abisror[1] | Estibaliz Lazaro[23] | Jean-Guillaume Lopez[24] | Alexandre Maria[25] | Wladimir Mauhin[26] | Julie Merindol[27] | Claire Merlot[28] | Tristan Mirault[29] | Laurent Pascal[30] | François Perrin[31] | Emmanuel Raffoux[32] | Ramy Rahme[33] | Damien Roos-Weil[34] | Benjamin Terrier[35] | Benjamin Thoreau[36] | Olivier Fain[1] | Pierre Fenaux[3,4] | Pierre Hirsch[37] | Vincent Jachiet[1,^^] | Jérôme Hadjadj[1,^^] | Arsène Mékinian[1,^^] | MINHEMON

Correspondence: Romain Stammler (romain.stammler@gmail.com)

[1]Service de Médecine Interne, Hôpital Saint-Antoine, AP-HP, Sorbonne Université, Paris, France
[2]Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, INSERM UMR 1163, Imagine Institute, University Paris Cité, Paris, France
[3]Hematology Department, AP-HP, Saint Louis Hospital, Paris, France
[4]INSERM U1342, Saint-Louis Research Institute and Paris Cité University, Paris, France
[5]French Reference Center for Mastocytosis (CEREMAST), Necker - Enfants Malades University Hospital, APHP, Paris Cité University, Paris, France
[6]Service de Génomique des Tumeurs et Pharmacologie, Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris, Paris, France
[7]Department of Internal Medicine, IUCT-Oncopole, Toulouse University Hospital (CHU-Toulouse), Toulouse, France
[8]Cancer Research Center of Toulouse, Unité Mixte de Recherche (UMR) 1037 INSERM, ERL5294 Centre National de La Recherche Scientifique, Toulouse, France
[9]School of Medicine, Université Toulouse III-Paul Sabatier, Toulouse, France
[10]Hematology Department, Centre Hospitalier Lyon Sud, Pierre-Bénite, France
[11]Department of Internal Medicine, Scorff-Lorient Hospital, Lorient, France
[12]Médecine Interne, Hôpital Robert Schuman, Metz, France
[13]Service d'Hématologie Clinique, Centre Hospitalier Régional et Universitaire de Brest, Brest, France
[14]Service de Médecine Interne, Centre Hospitalier de Libourne, Libourne, France
[15]Internal Medicine, Strasbourg University Hospital Center, Strasbourg, France
[16]Department of Internal Medicine and Hematology, Centre Hospitalier Rochefort, Rochefort, France
[17]Service de Médecine Interne, Centre Hospitalier de Dieppe, Dieppe, France
[18]Department of Medicine, Division of Hematology, CHU of Liège, Liège, Belgium
[19]Service d'Hématologie Clinique, Hôpital Saint-Louis, APHP, Paris, France
[20]The Internal Medicine Department, Groupe Hospitalier Saint-André, Bordeaux University Hospital, Bordeaux, France
[21]Department of Internal Medicine, Tenon Hospital, AP-HP, Sorbonne University, Paris, France
[22]Service d'Hématologie Biologique, APHP, Hôpital Cochin, Paris, France
[23]Department of Internal Medicine and Infectious Diseases, University Hospital of Bordeaux, Haut-Lévêque Hospital, Pessac, France
[24]Internal Medicine Department, Dupuytren University Hospital, Limoges, France

Myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) are heterogeneous clonal disorders that may be associated with immune-mediated inflammatory disorders (IMIDs), reported in up to 25% of patients.[1–4] The contribution of clonal hematopoiesis to systemic inflammation is increasingly recognized, exemplified by the recently described VEXAS syndrome.[5] Among recurrent genetic alterations in these myeloid neoplasms (MNs), isocitrate dehydrogenase (*IDH*1/2) mutations are present in 2%–12% of MDS and 4%–6% of CMML.[6,7] Beyond their leukemogenic role through 2-hydroxyglutarate–mediated epigenetic dysregulation, *IDH* mutations are enriched in patients with IMIDs (14%–20%), suggesting a contribution to immune dysregulation.[8,9] The clinical impact of IDH inhibition on inflammatory manifestations has never been addressed. In this retrospective multicenter study, we characterized *IDH*-mutated MN with IMIDs and highlighted the striking efficacy of IDH inhibitors on systemic inflammation.

We analyzed 50 patients with *IDH*-mutated MN and IMIDs (IDH^{mut}) and compared them to 61 patients with MN and IMIDs without *IDH* mutations (IDH^{wt} group). Clinical, biological, and immunological features, survival, and therapeutic responses were assessed. IMIDs' diagnoses were reviewed by three specialists and defined according to international criteria. Inflammatory responses were classified as complete (iCR) or partial (iPR), based on clinical signs, C-reactive protein (CRP) levels, and corticosteroid dose; overall response (iOR) referred to either iCR or iPR. Methodological details, including definitions of inflammatory manifestations, response criteria, and laboratory methods, are provided in the Supporting Information.

The IDH^{mut} group (50% male, median age 73 years [54–85]) included 36 (72%) patients with MDS, mostly with low blasts (69%) or increased blasts (25%), and 14 (28%) with CMML, mostly CMML-1 (93%) (Table 1). Abnormal cytogenetics were present in 10 (20%) patients, most frequently trisomy 8 ($n = 4$) and complex karyotype ($n = 2$). *IDH1* mutations were detected in 54%, *IDH2* in 44%, and both in 2%. In MDS, 78% were classified as low-risk according to the molecular international prognostic scoring system (IPSS-M) (≤0), while in CMML, 71% were classified as low-risk by chronic myelomonocytic leukemia-specific molecular prognostic scoring system (CPSS-Mol) (≤1). Inflammatory manifestations were dominated by musculoskeletal involvement (78%), mainly polyarthritis, followed by cutaneous manifestations (44%), mostly neutrophilic dermatosis, with 30% of patients presenting both. The most frequent IMIDs diagnoses were seronegative arthritis (34%), polymyalgia rheumatica (PMR, 26%), and giant cell arteritis (GCA, 16%). No significant differences were found between MDS and CMML patients, except for neoplasia-related hematologic features and a higher frequency of digestive involvement in CMML (Table S1). As expected from the higher prevalence of CMML, *IDH2*-mutated patients exhibited higher leukocyte, neutrophil, and monocyte counts, while CRP levels were lower compared with IDH1-mutated patients (Table S2).

Compared with the 61 IMIDs patients from the IDH^{wt} group (MDS 54%, CMML 46%), those in the IDH^{mut} group were more frequently female ($P = 0.009$) and older ($P = 0.04$) (Table 1). Musculoskeletal manifestations were significantly more common in the IDH^{mut} group (78% vs. 54%), whereas cutaneous, digestive, and renal manifestations were significantly less frequent. PMR was particularly enriched in the IDH^{mut} group (26% vs. 8%, $P = 0.02$), while GCA occurred more frequently only in the subgroup of IDH^{mut} patients with MDS (17% vs. 0%, $P = 0.02$). Consistent with a lower proportion of CMML, leukocyte, neutrophil, and monocyte counts were significantly reduced in the IDH^{mut} group. As previously reported,[10,11] comparison of the mutational landscape showed that *SRSF2* mutations were significantly more frequent ($P = 0.02$), mostly in the CMML group, and *TET2* mutations were less frequent ($P < 0.0001$) in both CMML and MDS IDH^{mut} group (Figure S1). Overall survival and leukemia-free survival were not statistically different between IDH^{mut} and IDH^{wt} groups, nor between *IDH1* and *IDH2*-mutated patients (Figures S2 and S3).

Cytokine profiling performed in 13 patients (4 MDS-IDH^{mut}, 2 CMML-IDH^{mut}, 4 MDS-IDH^{wt}, and 3 CMML-IDH^{wt}) with active IMIDs (Table S3) showed a significant broader upregulation of inflammatory cytokines in the IDH^{mut} group than in the IDH^{wt} group and in age- and sex-matched healthy controls (HCs), though only IFN-λ, IL-13, MIP-3β, and FASL reached statistical significance (Figures 1A and S4A,B). These cytokine alterations were accompanied by a marked reduction in circulating nonclassical monocytes in both IDH^{mut} and IDH^{wt} groups comparatively to HCs (Figure S4C,D). Due to the small sample size, no formal MDS/CMML comparisons were performed, but no apparent disease-related differences were observed. Supporting the role of monocytes in disease pathogenesis, Sanger sequencing of sorted cell populations in a patient with *IDH2*-mutated CMML and systemic granulomatosis showed restriction of the *IDH2* mutation to CD14+ monocytes (Figure S4E), with the same mutation subsequently identified in a skin lesion biopsy. An *IDH1* mutation was also detected in the temporal artery of a patient with GCA, supporting the contribution of clonal myeloid cells to tissue inflammation. Finally, as expected, elevated plasma 2-HG concentrations were observed exclusively in IDH^{mut} patients (Figure S4F), although no correlation was found between 2-HG levels and CRP or cytokine concentrations (Figure S5).

In the IDH^{mut} group, most patients initially responded to corticosteroids in their IMID manifestations but rapidly developed corticosteroid dependence. Subsequent use of corticosteroid-sparing treatments (such as targeted anti-

[25]Department of Internal Medicine-Multiorganic Diseases, Local Referral Center for Auto-Immune Diseases, Saint-Eloi Hospital, University Hospital Centre of Montpellier, Montpellier, France
[26]Department of Internal Medicine-Rheumatology, Referral Center for Lysosomal Diseases, filière G2M, GH Diaconesses, Croix Saint Simon Hospital, Paris, France
[27]Internal Medicine Department, University Hospital of Nice, Côte d'Azur University, Nice, Provence-Alpes-Côte d'Azur, France
[28]Service de Médecine Interne, Centre Hospitaliser d'Orléans, Orléans, France
[29]Service de Médecine Vasculaire et Centre de Référence des Maladies Artérielles Rares, AP-HP, Hôpital Européen Georges-Pompidou, Paris, France
[30]Service d'Onco-Hématologie Adulte, Hôpital Saint-Vincent de Paul, GH de l'institut Catholique de Lille, Lille, France
[31]Médecine Interne, Centre Hospitalier de Saint-Nazaire, Saint-Nazaire, France
[32]Service Hématologie Adultes, Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris, THEMA Saint-Louis Leukemia Institute, Université Paris Cité, Paris, France
[33]Hematology Department, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris, Bobigny, France
[34]Hematology, Pitié-Salpêtrière Hospital, Sorbonne Université, Paris, France
[35]Department of Internal Medicine, National Reference Center for Autoimmune Diseases, Hôpital Cochin, Assistance Publique Hôpitaux de Paris (AP-HP), Paris, France
[36]Service de Medecine Interne, Hôpital Bretonneau, Tours, France
[37]INSERM, Centre de Recherche Saint-Antoine, CRSA, AP-HP, SIRIC CURAMUS, Hôpital Saint-Antoine, Service d'Hématologie Biologique, Sorbonne Université, Paris, France
^Peter Chen and Orianne Debeaupuis contributed equally.
^^Vincent Jachiet, Jérôme Hadjadj, and Arsène Mékinian contributed equally.

TABLE 1 Characteristics of immune-mediated inflammatory disorder (IMID) patients with isocitrate dehydrogenase (*IDH*)-mutated versus *IDH*-wild type myeloid neoplasms. (continued on next page)

	IDH^{mut} (*n* = 50)	*IDH*^{wt} (*n* = 61)	MDS-*IDH*^{mut} (*n* = 36)	MDS-*IDH*^{wt} (*n* = 33)	CMML-*IDH*^{mut} (*n* = 14)	CMML-*IDH*^{wt} (*n* = 28)
Demographics						
Male sex	25 (50%)**	46 (75%)	16 (44%)*	25 (76%)	9 (64%)	21 (75%)
Age at MN diagnosis (years)	73 (54–85)*	69 (20–86)	74 (54–85)**	68 (32–81)	71 (54–85)	70 (20–86)
Hematological parameters						
Blood counts						
Hemoglobin (g/L)	10.8 (8–14.4)	10.3 (6–15.1)	10.8 (8–14.4)*	9.5 (7.4–13.7)	10.9 (8.5–13.3)	11.2 (6–15.1)
Platelets (G/L)	199 (24–961)**	153 (10–845)	199 (36–961)	154 (10–845)	198 (24–485)	153 (39–366)
Leukocytes (G/L)	3.5 (1.1–16)***	6 (2.1–91)	3.2 (1.1–10.3)***	5 (2.1–36)	7.3 (2.9–16)	13.4 (4.7–91)
Neutrophils (G/L)	1.2 (0.2–11.5)***	3.6 (0.3–56)	1 (0.2–7.6)***	3.4 (0.3–18.1)	3.8 (0.6–11.5)	4.7 (0.7–56)
Monocytes (G/L)	0.4 (0–5.1)**	0.9 (0.1–12)	0.2 (0–1.6)*	0.4 (0.1–2)	1.25 (1–5.1)	2.3 (1–12)
Bone marrow						
Dysgranulopoiesis	39/45 (87%)	14/21 (67%)	32/35 (91%)**	5/10 (50%)	7/10 (70%)	9/11 (82%)
Dyserythropoiesis	24/45 (53%)	5/14 (36%)	22/35 (63%)	3/8 (37%)	2/10 (20%)	2/6 (33%)
Dysmegakaryopoiesis	29/45 (64%)	6/14 (43%)	22/35 (63%)	5/8 (62%)	7/10 (70%)	1/6 (17%)
Bone marrow blasts (%)	1 (0–15)	1.7 (0–14)	1 (0–15)	1.5 (0–14)	1.5 (0–13)	2.5 (0–13)
Abnormal marrow cytogenetics	10 (20%)	22/60 (37%)	8 (22%)	13/32 (41%)	2 (14%)	9 (28%)
Trisomy 8	4/10 (40%)	6/23 (26%)	2/8 (25%)	1/13 (8%)	2/2 (100%)	5/9 (56%)
Complex karyotype[a]	2/10 (20%)	6/23 (26%)	2/8 (25%)	5/13 (38%)	0/2 (0%)	1/9 (11%)
Other	4/10 (40%)[b]	10/23 (43%)[c]	4/8 (50%)	7/13 (54%)	0/2 (0%)	3/9 (33%)
Prognostic scores						
Low IPSS-M (≤0)	-	-	28 (78%)	19/29 (65%)	-	-
Low CPSS-M (≤1)	-	-	-	-	10 (71%)	10/26 (38%)
IMID-related parameters						
Chronology						
IMID diagnosis before MN diagnosis	28/48 (58%)	37/61 (61%)	20/34 (59%)	23/33 (70%)	8/14 (57%)	14/28 (50%)
Concomitant IMID and MN diagnoses	10/48 (21%)	9/61 (15%)	7/34 (21%)	4/33 (12%)	3/14 (21%)	5/28 (18%)
IMID diagnosis after MN diagnosis	10/48 (21%)	15/61 (24%)	7/34 (21%)	6/33 (18%)	3/14 (21%)	9/28 (32%)
Interval between IMID and MN diagnoses (months)	18 (0–224)	11 (0–96)	24 (0–224)	11 (0–96)	17 (0–43)	15 (0–96)
Clinical features						
Musculoskeletal	39 (78%)**	33 (54%)	28 (78%)	21 (64%)	11 (79%)*	12 (43%)
Inflammatory arthralgia	20/39 (51%)	18/33 (54%)	16/28 (57%)	8/21 (38%)	4/11 (36%)	10/12 (83%)
Arthritis	19/39 (49%)	12/33 (36%)	12/28 (43%)	9/21 (43%)	7/11 (64%)	3/12 (25%)
Other	1/39 (3%)[d]	7/33 (21%)[e]	1/28 (4%)	6/21 (29%)	0/11 (0%)	1/12 (8%)
Skin	22 (44%)*	39 (64%)	17 (47%)	21 (64%)	5 (36%)	18 (64%)
Fever	17 (34%)	25 (41%)	14 (39%)	13 (39%)	3 (21%)	12 (43%)
Pulmonary	10 (20%)	10 (16%)	5 (14%)	6 (18%)	5 (36%)	4 (14%)
Ocular	7 (14%)	6 (10%)	3 (8%)	3 (9%)	4 (29%)	3 (11%)
Nervous system	6 (12%)	5 (8%)	4 (11%)	2 (6%)	2 (14%)	3 (11%)
Venous thrombosis	4 (8%)	3 (5%)	4 (11%)	1 (3%)	0 (0%)	2 (7%)
Digestive	2 (4%)*	12 (20%)	0 (0%)**	6 (18%)	2 (14%)	6 (21%)
Cardiac	1 (2%)	7 (11%)	0 (0%)	2 (6%)	1 (7%)	5 (18%)
Renal	0 (0%)**	8 (13%)	0 (0%)	2 (6%)	0 (0%)	6 (21%)
Chondritis	0 (0%)	4 (6%)	0 (0%)	2 (6%)	0 (0%)	2 (7%)

TABLE 1 (Continued)

	IDH^{mut} (*n* = 50)	*IDH*^{wt} (*n* = 61)	MDS-*IDH*^{mut} (*n* = 36)	MDS-*IDH*^{wt} (*n* = 33)	CMML-*IDH*^{mut} (*n* = 14)	CMML-*IDH*^{wt} (*n* = 28)
Biological features						
C-reactive protein during flare (mg/L)	40 (0–300)	62 (0–450)	37 (0–300)	71 (7–450)	40 (0–108)	60 (0–350)
IMID diagnoses						
Seronegative arthritis	17 (34%)	15 (25%)	13 (36%)	11 (33%)	4 (29%)	4 (14%)
Polymyalgia rheumatica	13 (26%)*	5 (8%)	9 (25%)	3 (9%)	4 (29%)	2 (7%)
Giant cell arteritis	8 (16%)	6 (10%)	6 (17%)*	0 (0%)	2 (14%)	6 (21%)
Other	12 (24%)[f]	8 (13%)[g]	7 (19%)	4 (12%)	5 (36%)	4 (14%)
Follow-up						
Median follow-up (months)	31 (1–166)	38 (1–123)	28 (1–134)	25 (1–123)	45 (4–166)	48 (1–122)
Alive at last follow-up	36 (72%)	36 (59%)	28 (78%)	20 (61%)	8 (57%)	16 (57%)
Progression to acute myeloid leukemia	10 (20%)	7 (11%)	7 (19%)	5 (15%)	3 (21%)	2 (7%)

Note: Continuous variables are presented as medians (range), while categorical variables are presented as counts (percentage).

Abbreviations: CMML, chronic myelomonocytic leukemia; CPSS-M, CMML-specific prognostic scoring system; IPSS-M, molecular International Prognostic Scoring System; MDS, myelodysplastic syndrome; MN, myeloid neoplasm.

[a]Complex karyotype (i.e., ≥3 anomalies).

[b]Other (*n* = 4) including del20q (*n* = 2), del5p (*n* = 1), and +19+21 (*n* = 1).

[c]Other (*n* = 10) including del20q (*n* = 3), −Y (*n* = 2), del5q (*n* = 1), −7 (*n* = 1), del7q (*n* = 1), and del4q (*n* = 1).

[d]Inflammatory back pain.

[e]Other (*n* = 7) including inflammatory back pain (*n* = 2) and myalgia (*n* = 5).

[f]Other (*n* = 12) including Sjogren syndrome (*n* = 4), systemic sclerosis (*n* = 2), inflammatory bowel disease (*n* = 3), rheumatoid arthritis (*n* = 2), and spondyloarthritis (*n* = 1).

[g]Other (*n* = 8) including Sjogren syndrome (*n* = 1) and inflammatory bowel disease (*n* = 7). Comparisons were performed between *IDH*^{mut} and *IDH*^{wt} groups. Statistical significance is indicated as follows:

*P-value ≤ 0.05; **P-value ≤ 0.01; ***P-value ≤ 0.001.

inflammatory therapies or hypomethylating agents) achieved only limited and unsustained benefit: interleukin-6 (IL-6) inhibitors (*n* = 9), IL-1 inhibitors (*n* = 3), tumor necrosis factor (TNF)-α inhibitors (*n* = 3), JAK inhibitors (*n* = 2), abatacept (*n* = 2), and azacitidine (*n* = 12) (Figure 1B). By contrast, 7 (14%) patients with active IMID were treated with oral IDH inhibitors, including 6 anti-IDH1 ivosidenib (500 mg/day) and 1 with anti-IDH2 enasidenib (100 mg/day) (Figure 1C). At IDH inhibitor onset, four patients were receiving concomitant corticosteroids (median dose 8.5 mg/day), one was on azacitidine (initiated simultaneously but discontinued after 1 month), and one was on ruxolitinib with a partial response. The median duration of IDH inhibitor therapy was 13 (3–40) months. The inflammatory overall response rate (iORR) was 86% at 3 months (57% iCR, 29% iPR), 83% at 6 months (33% iCR, 50% iPR), and 66% at 12 months (iCR 50%, 16% iPR). Corticosteroid doses decreased from a median of 8.5–5 mg/day between baseline and Month 12, while median CRP levels dropped from 93 to 6 mg/L (Figure 1C). All patients who achieved an inflammatory response also displayed a hematologic response (six complete, one partial). Clonal evolution assessed in two patients showed that clinical and CRP improvement correlated with a decrease in bone marrow blasts and *IDH* variant allele frequency (22%–11% and 31%–19%), suggesting a relationship between inflammatory activity and clonal burden (Figure S6). One illustrative patient with *IDH1*-mutated MDS and refractory PMR achieved clinical complete remission with ivosidenib, associated with normalization of CRP and a marked decline in IL-6, IL-18, cytotoxic mediators, and several chemoattractants (Figure 1D). In this patient, plasma 2-HG levels measured before and after 11 months of IDH inhibitor exhibited a clear decrease, concomitant with CRP reduction. Corticosteroids were the only concomitant treatment, and although the patient remained symptomatic on 15 mg/day at IDH inhibitor initiation, clinical remission was achieved with 5 mg/day after 11 months. IDH inhibitors were generally well tolerated. A single patient experienced chronic diarrhea. No additional safety concerns were observed.

This multicenter retrospective study provides valuable insight by identifying a distinct clinical and immunological phenotype of IMIDs associated with *IDH*-mutated MNs. Patients with *IDH* mutations were older, more frequently female, and predominantly presented with rheumatic manifestations, particularly seronegative arthritis and PMR-like syndromes, whereas cutaneous and digestive features were less common. Since cutaneous manifestations are unusual in rheumatoid arthritis or PMR, their association with rheumatic manifestations should raise suspicion of an underlying MN; the presence of hematologic abnormalities—such as cytopenias or monocytosis—should prompt systematic screening for somatic mutations.

IDH mutations have been shown to alter differentiation, epigenetic regulation, and immune signaling, notably by increasing sensitivity to inflammatory stimuli such as IL-1β and enhancing NF-κB–mediated cytokine activation.[12] They may also promote immune dysregulation through T-cell imbalance and 2-HG–mediated suppression of CD4/CD8 T-cell proliferation and activation.[8,13,14] Our exploratory analyses suggest a central role of innate immunity in *IDH*-mutated IMIDs, with pro-inflammatory cytokine upregulation, depletion of circulating nonclassical monocytes suggestive of tissue recruitment, and detection of *IDH* mutations within tissue-infiltrating monocytes supporting the role of clonal myeloid cells in driving peripheral inflammation.

The therapeutic management of IMIDs in MN is particularly challenging, as patients frequently develop corticosteroid dependence

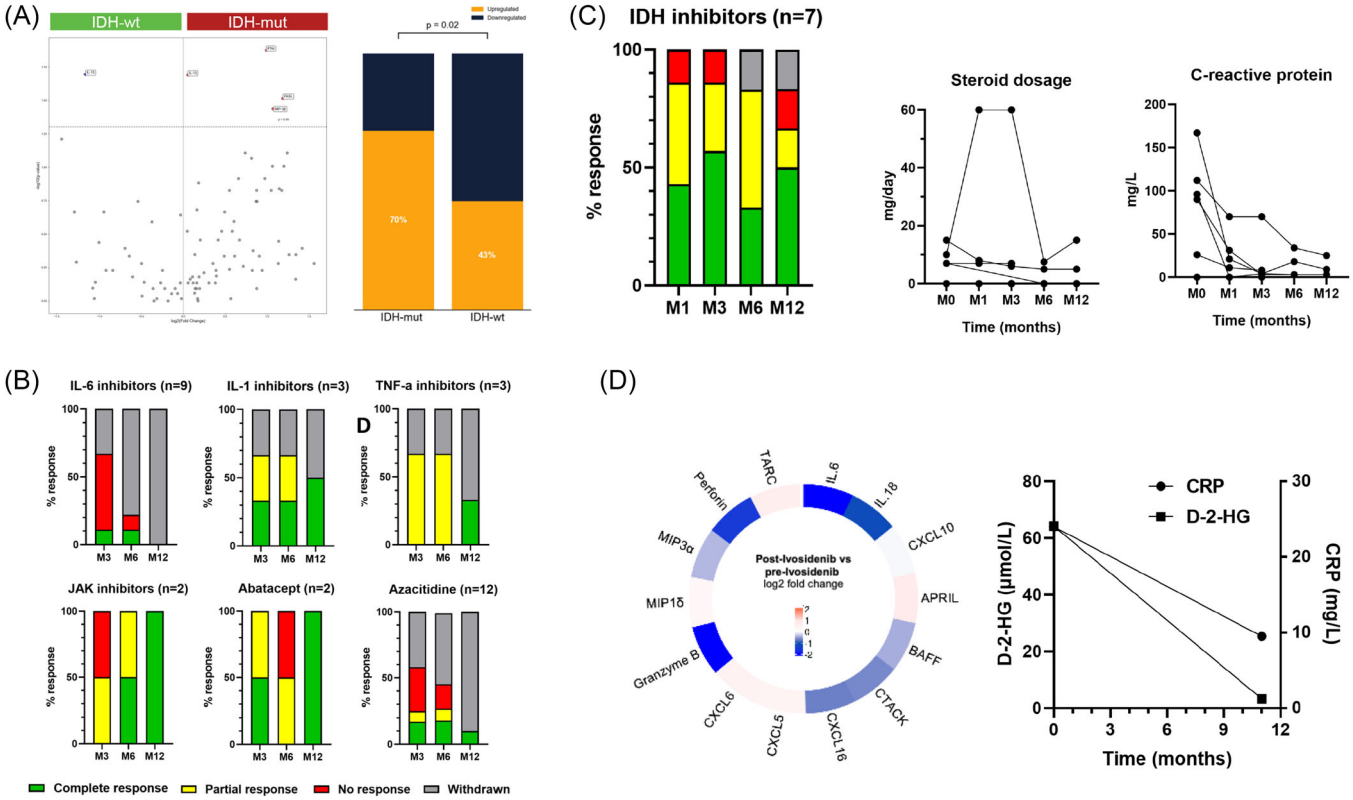

FIGURE 1 **Cytokine profiling in immune-mediated inflammatory disorder (IMID) patients with *IDH*^{mut} or *IDH*^{wt} myeloid neoplasms, and therapeutic efficacy of biotherapies and anti-IDH inhibitors in IMID-IDH^{mut} patients. (A)** Volcano plots showing upregulated (right) and downregulated (left) cytokines and chemokines between IDH^{mut} and IDH^{wt}. The green dashed line marks the significance threshold. Only significant cytokines are labeled. Global comparison of upregulated and downregulated cytokines between IDH^{mut} and IDH^{wt} groups. **(B)** Evolution of overall inflammatory response rates over time with biotherapies and azacitidine treatments. **(C)** Evolution of overall inflammatory response rates, steroid dosage, and C-reactive protein level over time with IDH inhibitors. **(D)** Cytokine profile pre- and post-ivosidenib (anti-IDH1) in one patient showing log2 fold changes in circulating cytokines and chemokines, with upregulated (red) and downregulated (blue) markers. D-2-HG and C-reactive protein (CRP) levels evolution under anti-IDH1 inhibitor in the same patient. IL, interleukin-6; TNF, tumor necrosis factor.

and experience only limited or unsustained benefit from targeted anti-inflammatory therapies, highlighting the need for novel treatments. Targeted IDH inhibitors have demonstrated hematologic efficacy in *IDH*-mutated MN, but their impact on inflammatory manifestations has not been explored. In our cohort, although the small sample size precludes drawing formal conclusions, IDH inhibitors were associated with favorable and sustained responses in IDH^{mut} patients, suggesting that these drugs may represent an innovative and safe therapeutic strategy addressing both the hematologic and inflammatory components of the disease.

In summary, this study identifies a distinct clinical and immunological phenotype of IMIDs associated with *IDH*-mutated MNs, characterized by predominant rheumatologic manifestations and a striking response to targeted IDH inhibition. These findings underscore the importance of considering both hematologic and immunologic dimensions in this population and provide a rationale for future studies evaluating strategies that target both clonal and inflammatory components. Larger prospective cohorts will be required to validate these observations and strengthen the conclusions.

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AUTHOR CONTRIBUTIONS

Romain Stammler: Conceptualization; investigation; writing—original draft; methodology; writing—review and editing; formal analysis. **Peter Chen**: Investigation. **Orianne Debeaupuis**: Investigation. **Lin-Pierre Zhao**: Investigation; methodology. **Mirabelle Ruyer-Thompson**: Investigation. **Eve Zakine**: Investigation. **Julien Rossignol**: Investigation. **Lauriane Goldwirt**: Investigation. **Thibault Comont**: Investigation. **Maël Heiblig**: Investigation. **Lionel Adès**: Investigation; methodology. **Marie Sebert**: Investigation; methodology. **Jean-Sébastien Allain**: Investigation. **Julien Campagne**: Investigation. **Marie-Anne Couturier**: Investigation. **Marina Cumin**: Investigation. **Marie-Caroline Dalmas**: Investigation. **Guillaume Denis**: Investigation. **Cécile Devloo**: Investigation. **Adrien De Voeght**: Investigation. **Louis Drevon**: Investigation. **Pierre Duffau**: Investigation. **Sophie Georgin-Lavialle**: Investigation. **Delphine Gobert**: Investigation. **Olivier Kosmider**: Investigation. **Frédéric Rieux-Laucat**: Investigation. **Noémie Abisror**: Investigation. **Estibaliz Lazaro**: Investigation. **Jean-Guillaume Lopez**: Investigation. **Alexandre Maria**: Investigation. **Wladimir Mauhin**: Investigation. **Julie Merindol**: Investigation. **Claire Merlot**: Investigation. **Tristan Mirault**: Investigation. **Laurent Pascal**: Investigation. **François Perrin**: Investigation. **Emmanuel Raffoux**: Investigation. **Ramy Rahme**: Investigation. **Damien Roos-Weil**: Investigation. **Benjamin Terrier**: Investigation. **Benjamin Thoreau**: Investigation. **Olivier Fain**: Investigation. **Pierre Fenaux**: Investigation; methodology. **Pierre**

Hirsch: Investigation; methodology. **Vincent Jachiet**: Investigation; conceptualization; writing—original draft; methodology; validation; supervision; writing—review and editing. **Jérôme Hadjadj**: Supervision; conceptualization; investigation; writing—original draft; methodology; validation; writing—review and editing. **Arsène Mékinian**: Conceptualization; funding acquisition; writing—original draft; writing—review and editing; visualization; methodology; supervision.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was conducted in accordance with the Good Clinical Practice protocol and the tenets of the Declaration of Helsinki principles, and was approved by the local Institutional Review Board (IRB 00006477; N° CER-2022-194).

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

ORCID

Romain Stammler https://orcid.org/0000-0002-0533-5964
Julien Rossignol https://orcid.org/0000-0003-3052-1424
Thibault Comont https://orcid.org/0000-0002-6891-9238
Maël Heiblig https://orcid.org/0000-0003-1682-8657

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