Blood Reviews 58 (2023) 101014

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Biologic therapies for hypereosinophilic disorders: From tyrosine kinase inhibitors to monoclonal antibodies. Towards an increasingly customized management?

Alessandra Iurlo [a,*], Daniele Cattaneo [a,b]

[a] Hematology Division, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[b] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

ARTICLE INFO

Keywords:
Hypereosinophilic syndromes
PDGFRA/B
Chronic eosinophilic leukemia
Tyrosine kinase inhibitors
Monoclonal antibodies
Targeted therapy

ABSTRACT

Hypereosinophilic syndromes (HES) encompass a wide range of disorders characterized by persistent peripheral blood hypereosinophilia (HE) (i.e., an eosinophil count $\geq 1.5 \times 10^9$/L and $\geq$ 10% eosinophils preferably with a minimal duration of 6 months if documentation is available) associated with organ damage and/or dysfunction attributable to tissue eosinophilic infiltrate and release of granule contents.

In most cases, HE is associated with atopic conditions/allergies, parasitic infections, medications, autoimmune disorders and/or solid tumors in most cases. More rarely, it can be one of the dominant manifestations of an underlying myeloid/lymphoid neoplasm.

With regard to hematological forms, in recent decades the advances in understanding the pathogenic aspects of HES have led to a growing interest in these diseases, and in the 2016 WHO classification multiple subgroups were defined according to the molecular profile with the aim of better characterizing these syndromes and establishing which patients will benefit from specific pharmacological targeted therapies.

This review article will provide a comprehensive overview of possible therapeutic approaches for HES in the light of each specific molecular alteration, considering both tyrosine kinase inhibitors and monoclonal antibodies, either implemented in clinical practice or currently still under development.

1. Introduction

Hypereosinophilic syndromes (HES) encompass a wide range of disorders characterized by persistent peripheral blood (PB) hypereosinophilia (HE) [i.e., an absolute eosinophil count (AEC) $\geq 1.5 \times 10^9$/L and $\geq$ 10% eosinophils preferably with a minimal duration of 6 months if documentation is available] associated with organ damage and/or dysfunction attributable to tissue eosinophilic infiltrate and release of granule contents. Its severity was arbitrarily divided into mild (AEC from the upper limit of normal to 1.5×10^9/L), moderate (AEC 1.5–5 $\times 10^9$/L) and severe (AEC >5 $\times 10^9$/L) [1–3]. The incidence and prevalence of HES are not well characterized, but it is considered a rare condition and the age-adjusted incidence rate is approximately 0.4 per 1.000.000 person-years [4].

In most cases, HE is associated with allergy/atopy and hypersensitivity conditions, infections, particularly tissue-invasive parasites, drug reactions, collagen-vascular disease, pulmonary eosinophilic diseases, allergic gastroenteritis (with associated peripheral eosinophilia), and metabolic conditions such as adrenal insufficiency, or solid tumors. More rarely, it can be one of the dominant manifestations of a primary bone marrow (BM) disorder, particularly the lymphocyte-variant (L-HES), defined by immunophenotypic detection of an abnormal T-cell population with or without T-cell receptor clonality by molecular analysis.

Furthermore, as large retrospective studies have shown that, regardless of etiology, approximately 5% of all HE cases months to years later (median time, 30 months) will eventually develop a hematological malignancy, all of these patients should be regularly monitored for clinical and laboratory tests suggesting this possible evolution [5,6].

With regard to hematological forms, in recent decades the progress in understanding the pathogenic aspects of HES has led to a growing interest in these diseases [7]. After the evaluation of secondary causes of

* Corresponding author at: Hematology Division, Myeloproliferative Syndromes Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122 Milano, Italy.
E-mail address: alessandra.iurlo@policlinico.mi.it (A. Iurlo).

https://doi.org/10.1016/j.blre.2022.101014

Available online 17 September 2022

eosinophilia, the 2016 WHO approves a semi-molecular classification scheme of the disease subtypes, including the following main categories (Table 1): 1) myeloid/lymphoid neoplasms with eosinophilia and *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement or with *PCM1-JAK2* (the latter still representing a provisional entity); 2) myeloproliferative neoplasm (MPN) subtype: chronic eosinophilic leukemia, not otherwise specified (CEL, NOS); and 3) idiopathic HES, which is a diagnosis of exclusion [8].

More recently, the upcoming 5th edition of the WHO Classification of Hematolymphoid Tumors has introduced several changes to the CEL diagnostic criteria, with the addition, among other things, of requirement for both clonality and abnormal BM morphology (e.g., megakaryocytic or erythroid dysplasia), also leading to the omission of the qualifier "not otherwise specified" from the name [9]. In contrast, the contemporary International Consensus Classification of Myeloid and Lymphoid Neoplasms maintained the same nomenclature as CEL, NOS, while refined the diagnostic criteria for idiopathic HES, emphasizing the importance of the absence of any molecular genetic clonal abnormality, with the caveat of clonal hematopoiesis of indeterminate potential [10].

Once secondary causes of eosinophilia are excluded, the diagnostic work-up of primary HES is based on examination of PB smear and blood tests (e.g., elevated serum B12, or tryptase level) in combination with BM morphological analysis, standard cytogenetic techniques, fluorescence in-situ hybridization (FISH), flow immunocytometry, evaluation of T-cell clonality, and molecular analysis (including next-generation sequencing in selected cases) to detect histopathological or molecular evidence of acute or chronic myeloid or lymphoid neoplasms [11]. Consequently, although the classification of myeloid neoplasms with eosinophilia has increasingly been based on molecular markers, their diagnosis must still be anchored to a combination of histomorphology and clinical-laboratory criteria.

Table 1
2016 WHO classification of hypereosinophilic syndromes.

Clinical entities	Diagnostic criteria
Idiopathic HES	Exclusion of the following: 1) Reactive eosinophilia 2) L-HES 3) CEL, NOS 4) eosinophilia associated with WHO-defined myeloid malignancies (e.g., MDS, MPN, MDS/MPN, or AML) 5) eosinophilia-associated MPN or AML/ALL with rearrangements of *PDGFRA*, *PDGFRB*, or *FGFR1* or with *PCM1-JAK2* 6) AEC $\geq 1.5 \times 10^9$/L for at least 6 months (tissue damage must be present)
CEL, NOS	1) eosinophilia (AEC $\geq 1.5 \times 10^9$/L) 2) Not meeting WHO criteria for *BCR-ABL1*-positive CML, PV, ET, PMF, CNL, CMML, or aCML 3) no rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*; no *PCM1-JAK2*, *ETV6-JAK2*, or *BCR-JAK2* fusion gene 4) blast cell count in the PB and BM <20%, and inv.(16)(p13.1q22), t(16;16)(p13;q22) or other diagnostic features of AML are absent 5) clonal cytogenetic or molecular abnormalities, or blast cells ≥2% in the PB or > 5% in the BM
Myeloid/lymphoid neoplasms with eosinophilia and *PDGFRA* rearrangement	1) myeloid/lymphoid neoplasm, usually with prominent eosinophilia 2) presence of a *FIP1L1-PDGFRA* fusion gene or a variant fusion gene with rearrangement of *PDGFRA*
Myeloid/lymphoid neoplasms with eosinophilia and *PDGFRB* rearrangement	1) myeloid/lymphoid neoplasm, often with prominent eosinophilia and sometimes with neutrophilia or monocytosis 2) presence of t(8;12) or a variant translocation or demonstration of an *ETV6-PDGFRB* fusion gene or rearrangement of *PDGFRB*
Myeloid/lymphoid neoplasms with eosinophilia and *FGFR1* rearrangement	1) MPN or MDS/MPN with prominent eosinophilia, and sometimes with neutrophilia or monocytosis or AML or precursor T-cell or precursor B-cell lymphoblastic leukemia/lymphoma or mixed phenotype acute leukemia 2) presence of t(8;13) or a variant translocation leading to *FGFR1* rearrangement demonstrated in myeloid cells, lymphoblasts, or both
Myeloid/lymphoid neoplasms with eosinophilia and *PCM1-JAK2*	1) myeloid or lymphoid neoplasm, often with prominent eosinophilia 2) presence of t(8;9) or a variant translocation leading to *JAK2* rearrangement

Abbreviations: MPN, myeloproliferative neoplasm; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; AEC, absolute eosinophilic count; CML, chronic myeloid leukemia; PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; CNL, chronic neutrophilic leukemia; CMML, chronic myelomonocytic leukemia; aCML, atypical chronic myeloid leukemia; PB, peripheral blood; BM, bone marrow; ALL, acute lymphoblastic leukemia.

2. Therapeutic options

Therapy should be directed, if possible, to the underlying etiology of HES (Table 2) [12]. As there are inadequate data to support therapy initiation based on a specific AEC alone, HES must be treated promptly and aggressively to reduce potential morbidity and mortality related to eosinophil-mediated organ damage.

2.1. Tyrosine kinase inhibitors

The initial use of tyrosine kinase inhibitors (TKIs) for the treatment of HES showing signs suggestive of MPN was based empirically on common features with chronic myeloid leukemia (CML), and rapid and complete hematological responses (CHR) to imatinib, a first-generation TKI, have been reported in early investigations on small series of patients [13,14].

2.1.1. Imatinib

Today, imatinib is the only TKI approved by FDA for HES therapy as it represents the drug of choice for myeloid neoplasms with eosinophilia and *PDGFRA/B* rearrangements [11,15–17].

Interestingly, due to the increased sensitivity of *FIP1L1-PDGFRA* compared to the *BCR-ABL1* fusion transcript, imatinib often induces remissions even at lower dosages than those used for CML, typically 100 mg daily [18].

2.1.1.1. Myeloid neoplasms with eosinophilia and FIP1L1-PDGFRA rearrangement: induction of remission and maintenance. Several studies have reported a high rate of complete and lasting hematological and molecular remissions during imatinib treatment in the dose range of 100–400 mg per day [18–27], although there is still a risk of relapse after imatinib discontinuation [28–31]. However, maintenance doses of 100 to 200 mg weekly have been shown to sustain a complete response [23].

Complete molecular response (CMR) was first reported by the National Institutes of Health (NIH) group in a series of seven patients with HES – myeloproliferative variant treated at a dose of 300–400 mg per day. Resolution of eosinophilia with clinical improvement was observed in all subjects and molecular remission was achieved with disappearance of detectable *FIP1L1-PDGFRA* transcript in five of the six patients tested [19].

In an Italian prospective cohort study, 27 subjects with *FIP1L1-PDGFRA*-rearranged HES were treated with imatinib 100 to 400 mg daily. All cases achieved a CHR and became negative for the fusion transcript by RT-PCR. With a median follow-up of 25 months, they

Table 2
Targeted therapeutic options.

DRUG	Therapeutic target	Dose	Number of patients	Results	Follow-up	Reference
TKIs						
Imatinib	*PDGFRA/B*	100–400 mg/day	*N* = 7	CHR 100%, CMR 83%	3 months	[19]
			N = 27	CHR 100%, CMR 100%	25 months	[20]
			N = 44	CHR 100%, CMR 95%	52 months	[22]
			N = 18	CHR 94%, CMR 100%	73 months	[25]
			N = 33	CHR 94%, CMR 97%	43 months	[26]
			N = 12	CMR 100%	65 months	[41]
Ruxolitinib	JAK-STAT pathway	20 mg BID	N = 2	CHR 100%	12 months	[57]
			N = 5	CHR 100%	NR	[60]
			N = 9	CHR 55%, CCyR 22%	36 months	[61]
Monoclonal antibodies						
Mepolizumab	IL-5	100–300 mg every 4 weeks	*N* = 43	CHR 95%	2 months	[78]
			N = 35	CHR 57%	NR	[81]
			N = 108	CHR 92%	8 months	[82]
			N = 400	ORR 55%	12 months	[89]
Benralizumab	IL-5Rα	30 mg every 4 weeks	*N* = 20	ORR 90%	3 months	[91]
			N = 20	CHR 75%	12 months	[92]
Alemtuzumab	CD52	5–30 mg 1 to 3 times weekly	N = 12	CHR 83%	16.5 months	[105]

Abbreviations: CHR, complete hematological response; CMR, complete molecular response; CCyR, complete cytogenetic response; ORR, overall response rate.

remained on CHR and RT-PCR negative while continuing treatment at the same daily dose [20].

Another European study using serial RT-Q-PCR prospectively evaluated the kinetics of molecular response to imatinib (100 to 400 mg per day) in patients with elevated *FIP1L1-PDGFRA* levels before treatment. Overall, all 11 evaluable subjects achieved at least a 3-log reduction in fusion transcripts from pretreatment level within 12 months, with CMR in nine cases [18].

Similarly, in 16 *FIP1L1-PDGFRA*-positive patients treated with imatinib at a daily dose of 100 to 400 mg, CHR was obtained in all cases after a median of 0.8 months and CMR in 75% of cases within 6 months and in 87% within 12 months. All subjects were maintained on imatinib treatment, most at 100 mg daily, with no molecular relapse at a median follow-up of 26.7 months [21].

The French eosinophil network conducted a retrospective survey on 44 *FIP1L1-PDGFRA*-positive subjects. Complete hematologic response was achieved in all patients, and CMR in 95% of subjects at a mean starting dose of imatinib of 165 mg/day. In 29 patients the mean daily maintenance dose was tapered to 58 mg without cases of resistance at a median follow-up of 52.3 months [22].

The efficacy of low-dose regimens for both induction and maintenance of CHR and CMR was also confirmed by two Polish reports on *FIP1L1-PDGFRA*-positive patients [23,24] and a Mayo Clinic study on subjects with *FIP1L1-PDGFRA*-mutated eosinophilia with excellent disease control and durable remissions maintained at dosages ranging from 100 mg/day to 100 mg/week [25].

In a Chinese study of 33 consecutive *FIP1L1-PDGFRA*-mutated patients treated at an initial daily dose of 100 (30 cases) or 200 mg (three cases) a high rate of CHR and CMR (94% and 97%, respectively) has been achieved. Twenty-four patients received maintenance treatment of 50 mg/week to 100 mg daily with a median duration of 43 months. Of the eight subjects who discontinued imatinib, four relapsed 2 to 48 months after stopping treatment [26].

The Polish hypereosinophilic syndrome study group recently updated its experience on 32 cases of *FIP1L1-PDGFRA*-mutated HES treated with imatinib. The starting dosage was 100 mg/day in 26 subjects and 400 mg/day in the remaining six. Complete molecular response was achieved after a median of 9 months with no difference between patients receiving 100 mg/day or 400 mg/day. The maintenance dosage ranged from 400 mg daily to 100 mg weekly, with a median duration of CHR and CMR of 11.5 and 9.8 years, respectively. No patient exhibited drug resistance or had a transformation into acute myeloid leukemia (AML). Five of seven patients relapsed within 12 months from treatment discontinuation, but a second CHR and CMR were obtained with imatinib resumption. Interestingly, two patients remained in remission for over 7 years after imatinib cessation [27].

2.1.1.2. Myeloid neoplasms with eosinophilia and FIP1L1-PDGFRA rearrangement: treatment discontinuation. The duration of imatinib excellent results prompted researchers to evaluate the feasibility of treatment discontinuation. However, outcome data frequently relied on a limited number of patients and reveal significant heterogeneity in relapse-free survival (RFS) [27–31].

A prospective dose de-escalation study enrolled five *FIP1L1-PDGFRA*-positive patients after at least one year in clinical, hematologic, and molecular remission on imatinib (300–400 mg daily). Two patients with a history of life-threatening cardiac involvement were maintained on imatinib 300 to 400 mg daily and served as a control population. Molecular relapse occurred only in subjects with a reduced dosage schedule; however, none developed recurrent symptoms and AEC remained suppressed. In all cases, resuming treatment at the previous effective dose led to molecular remission [28].

A Polish imatinib cessation trial enrolled seven patients with *FIP1L1-PDGFRA*-positive HES in CHR and CMR. The induction dosage was 100 mg daily in six patients and 400 mg daily in one. After CMR was achieved, all cases were shifted to a maintenance dose of 100 mg weekly. Treatment discontinuation was performed at a median of 6.6 years after initiation of imatinib. While four patients experienced molecular relapse after a median of 5.6 months, three subjects remained in CMR for a median of 65.9 months. There was no difference in median duration of CMR between relapsed and non-relapsed cases. Relapse-free survival was 42% at 2 years. Importantly, all patients retained prior sensitivity upon restarting imatinib [29].

In a retrospective French multicenter study on 44 *FIP1L1-PDGFRA*-positive patients, imatinib was stopped in eleven subjects. While six of them subsequently relapsed 1 to 27 months after drug discontinuation, five remained in CHR or CMR after a median follow-up of 31 months. Interestingly, duration of treatment prior to discontinuation did not differ between these two groups. Relapse free survival was 61% at 1 year and 42% at 2 years [22].

A recent German report analyzed the clinical and molecular follow-up of 12 cases of *FIP1L1-PDGFRA*–positive myeloid/lymphoid neoplasms with eosinophilia in chronic phase that discontinued imatinib after achieving CMR. Median duration of imatinib treatment and CMR before discontinuation was 80 and 66 months, respectively. While molecular relapse was observed in four patients after 10, 22 ($n = 2$), and 24 months, eight patients were still in CMR after a median follow-up of 17 months. Molecular RFS was 91% at 12 months and 65% at 24 months. There were no significant differences in duration of imatinib treatment or CMR before drug discontinuation between patients with and without

molecular relapse [30].

The French eosinophil network also recently reported a retrospective nationwide study on 148 imatinib-treated cases of *FIP1L1-PDGFRA*-positive myeloid neoplasm. All patients achieved CHR and CMR (when tested, $n = 84$). Forty-six patients discontinued imatinib and 20 (57%) relapsed. In multivariate analysis, time to imatinib initiation and duration of treatment were independent risk factors for relapse after drug discontinuation. After a median follow-up of 80 months, the 1, 5- and 10-year overall survival rates were 99%, 95% and 84%, respectively [31].

Although the above-mentioned findings suggest that treatment-free remission can be achieved in at least a proportion of imatinib-treated *FIP1L1-PDGFRA*-mutated HES, it is still unclear which factors predict long-term CMR and therefore imatinib discontinuation should generally be undertaken only in the context of clinical trials or registries.

2.1.1.3. Myeloid neoplasms with eosinophilia and FIP1L1-PDGFRA rearrangement: resistance to imatinib. Acquired resistance to imatinib of *FIP1L1-PDGFRA*-positive HES is a rare event; for example, in a German-wide registry of 57 patients treated with imatinib for a median of 36 months, only one case of secondary resistance was identified [32]. This is likely due to the fact that the PDGFR kinase domain contains a limited number of residues where exchanges could critically impair sensitivity to PDGFR kinase inhibitors [33].

Although two other drug-resistant mutants, D842V and S601P, have been identified [34], relapse during imatinib treatment is usually due to the T674I mutation in the ATP-binding region of *PDGFRA*, as originally reported by Cools et al. [35].

Although analogous to the T315I *ABL1* mutation in CML that confers resistance to imatinib, dasatinib, nilotinib and bosutinib [36], the T674I mutant can still respond in cell lines, transfected cells and in mouse models to nilotinib, midostaurin, sunitinib and sorafenib [32,34].

Despite these promising results, the clinical efficacy of these drugs as second-line treatment has proved modest possibly due to the presence of additional molecular abnormalities that confer resistance [32].

A patient with T674I *FIP1L1-PDGFRA* mutation in blast crisis had a clinical response to sorafenib, however short-lasting due to the rapid onset of a D842V *FIP1L1-PDGFRA* mutation highly resistant to sorafenib, imatinib, dasatinib and midostaurin [37]. In a further case of secondary resistance involving the T674I mutation, first nilotinib and then sorafenib did not obtain any response [32]. Although drugs with more potent activity against T674I and D842V mutations are being developed, currently in this clinical setting only allogeneic stem cell transplantation (ASCT) can extend disease-free survival.

Primary resistance to imatinib was also described in a *FIP1L1-PDGFRA*–positive patient in chronic phase and was related to a double S601P/L629P mutation that does not interfere with drug binding but rather increases target protein stability [38,39].

2.1.1.4. Myeloid neoplasms with eosinophilia and FIP1L1-PDGFRA rearrangement in blast phase. Imatinib activity has been reported not only in myeloid/lymphoid neoplasms with eosinophilia and *FIP1L1-PDGFRA* rearrangement in chronic phase but also in the blast phase of the disease.

In a series of 17 patients with eosinophilia-associated myeloid/lymphoid neoplasms with PDGFR rearrangement primarily diagnosed in blast phase, some of which mimic de novo AML or T-cell non-Hodgkin lymphoma (NHL), nine subjects with no initial knowledge of the underlying fusion gene were initially treated with chemotherapy and imatinib was started only upon subsequent identification of the *PDGFR* mutation. The eight remaining cases, known carriers of the rearrangement already at the time of diagnosis, started directly with imatinib. Overall, CHR was achieved in all patients and CMR was detected in all 12 *FIP1L1-PDGFRA*-positive cases; one patient died from a cerebral hemorrhage and the remaining eleven were in sustained CMR for a median of 65 months [40,41].

These data, which show that even highly aggressive neoplasms can be successfully treated with imatinib, highlight the importance of searching for *PDGFR* fusion genes in all hematological malignancies associated with eosinophilia in order to identify patients potentially eligible for TKI therapy.

2.1.1.5. Myeloid neoplasms with eosinophilia and PDGFRB rearrangement. Imatinib remains effective even in chronic-phase myeloid neoplasms with eosinophilia and *PDGFRB* rearrangement, typically at a daily dose of 400 mg [42].

In a series of twelve patients with *BCR-ABL1*-negative chronic MPNs treated with imatinib for a median of 47 months, eleven had a prompt response with disappearance of eosinophilia and ten achieved complete resolution of the cytogenetic abnormalities and decrease or disappearance of fusion transcripts, with a median overall survival of 65 months from diagnosis [43].

In an updated analysis of a cohort of 26 cases of myeloid neoplasms with eosinophilia treated with imatinib for a median of 6.6 years, the 10-year overall survival rate was 90% and the 6-year progression-free survival 88%. Importantly, no patients who achieved a complete cytogenetic ($n = 13$) or molecular ($n = 8$) remission lost response or progressed to blast phase [44].

A German study evaluated 22 patients with myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRB* on imatinib (100–400 mg daily). All chronic-phase subjects achieved CHR after a median of 2 months and 86% of these patients also obtained CMR after a median of 19 months. In five blast-phase patients, therapies administered included combinations of imatinib, intensive chemotherapy, and/or ASCT. Overall, after a median duration of treatment of 71 months the 5-year overall survival rate was 83% [45].

Imatinib also induced rapid and lasting complete remissions in three patients with eosinophilia-associated MPNs, each of whom harbored an uncommon fusion gene, *MPRIP-PDGFRB*, *CPSF6-PDGFRB* and *GOLGB1-PDGFRB*, respectively [46].

2.1.1.6. PDGFR-unmutated HES. In most patients with unknown or unmutated *FIP1L1-PDGFRA* HES imatinib partly maintains its efficacy, however higher dosages are required to achieve activity and responses are generally transient.

Indeed, two large prospective studies reported response rates between 14% and 40% [20,21], and in the pivotal study by Cools et al. among the nine imatinib-treated cases with responses lasting more than three months, only five had a detectable *FIP1L1-PDGFRA* fusion gene [35].

In a MD Anderson series of 18 patients with unknown or unmutated *FIP1L1-PDGFRA* HES, two cases achieved a partial response and one subject a CHR lasting 16 months at a daily imatinib dosage of 100 mg. All other patients were unresponsive even at daily dose escalated at 400 mg, confirming low sensitivity to imatinib of *PDGFRA*-unmutated HES [47].

In a Polish report 17 unmutated HES patients were treated with imatinib 100–400 mg/day. Only four cases achieved a response, including one with a duration of >11 years. Interestingly, all responders were male and in three out of four subjects the maintenance dose was 100 mg weekly [48].

It has been suggested that a myeloproliferative phenotype can predict response to imatinib in *PDGFRA*-negative HES. In a prospective-retrospective study that recruited 16 *PDGFRA*-positive and 29 *PDGFRA*-negative HES, all positive cases demonstrated a rapid and dramatic response to imatinib while the response rate was 54% in *PDGFRA*-negative patients showing at least four myeloproliferative features and 0% in subjects with fewer than four of these criteria [49].

Finally, in a small series of five patients with CEL, NOS carrying the *KIT*M541L mutation low-dose (100 mg daily orally) imatinib resulted in persistent CHR (median follow-up 74 months) [50,51]. Consequently, it

is recommended to search for the *KIT*M541L mutation in all *PDGFRA/B*-negative patients to identify cases that could benefit from this therapy.

2.1.1.7. Imatinib safety profile. The safety profile of imatinib in eosinophilic MPNs confirms the good tolerability reported in CML patients. Although a few cases of left ventricular dysfunction have been reported within the first weeks of treatment, serial evaluation of cardiac troponin T serum concentrations may be useful in predicting cardiac toxicity [52,53]. Interestingly, systemic corticosteroid (CS) therapy can reverse cardiogenic shock [53]. Consequently, concomitant use of short-term CS a few days before or during the first weeks of imatinib therapy may be considered.

2.1.2. Ruxolitinib

In recent years, some FDA-approved JAK inhibitors have been tested in HES, especially in those cases associated with gain-of-function mutations involved in the JAK/STAT signaling pathway [54].

In particular, the importance of ruxolitinib, an oral JAK1/2 inhibitor, has been highlighted by several reports. Ruxolitinib has been successfully used to treat a familial form of HES with immune dysregulation caused by a gain-of-function *JAK1* mutation [55], as well as a *PCM1-JAK2*-positive case that achieved eosinophils normalization and a complete cytogenetic response (CCyR) [56].

Similarly, two patients with myeloid neoplasms and a *PCM1-JAK2* or a *BCR-JAK2* fusion gene obtained a complete clinical, hematological, and cytogenetic response after 12 months of ruxolitinib treatment. Remission, however, was only short-term due to relapse which occurred after 18 and 24 months respectively, making ASCT indispensable in both cases [57].

In contrast to this report, two cases of myeloid neoplasms with *PCM1-JAK2* fusion gene treated with ruxolitinib achieved CHR, CCyR, and marked reduction in *PCM1-JAK2* fusion transcript lasting 36 and 46 months, respectively [58,59].

In addition, five idiopathic HES or L-HES patients with skin involvement were successfully treated in an open-label study with tofacitinib, a JAK1/3 inhibitor, or ruxolitinib, both showing CS-sparing activity and leading to near-complete resolution of skin lesions and normalization of AEC [60].

In a recent updated cohort of nine myeloid neoplasms with *PCM1-JAK2* ($n = 8$) or *BCR-JAK2* ($n = 1$) fusion genes, all treated with ruxolitinib, hematological and cytogenetic remissions were achieved in 5/9 and 2/9 cases, respectively. However, ruxolitinib was discontinued in eight subjects due to primary resistance, progression, or planned ASCT. At a median of 36 months after diagnosis, five of nine patients were alive, one still on ruxolitinib and four after ASCT [61].

The molecular basis for acquired resistance to ruxolitinib in *JAK2*-driven hematological malignancies is still poorly understood. In a patient with a *BCR–JAK2*-positive MPN who initially achieved a hematological response under ruxolitinib, however rapidly progressing to lymphoid blast phase, this transformation was associated with the detection of an *IKZF1* deletion, upregulation of IL-7R and CRLF2 RNA expression, and adaptation to an activated B-cell receptor (BCR)-like signaling phenotype, a potential mechanism of acquired ruxolitinib resistance [62].

2.1.3. Other tyrosine kinase inhibitors

2.1.3.1. FGFR1-rearranged myeloid/lymphoid neoplasms with eosinophilia. Unlike cases associated with *PDGFRA/B* rearrangements, myeloid/lymphoid neoplasm with rearranged *FGFR1* are resistant not only to imatinib and second- or third-generation TKIs such as nilotinib, dasatinib and ponatinib, but also poorly responsive to other agents, such as midostaurin.

While in *FGFR1*-positive cell lines and primary cell cultures ponatinib was able to induce apoptosis and reduce the number of colonies as well as prolong the survival of transplanted mice [63,64], in the clinical setting its activity was unexpectedly scarce.

In a series of seven consecutive *FGFR1*-positive myeloid neoplasms with eosinophilia patients initially treated with chemotherapy-based regimens and/or high-dose chemotherapy, ponatinib at a dose of 30–45 mg/day achieved a temporary partial hematological response in six cases and a partial cytogenetic response in one subject. Four patients underwent ASCT and were in CMR and alive after a median time of 13 months after transplant [65].

Midostaurin, while active in murine models, when administered to a subject with *FGFR1*-positive MPN induced a response on leukocytosis, lymphadenopathy and splenomegaly without any cytogenetic remission [66]. Consequently, high-dose chemotherapy followed by ASCT is usually required to ameliorate patients' survival [67].

Recently, promising results have been reported with futibatinib, a selective oral small molecule inhibitor of FGFR1–4. In one case of *FGFR1*-driven myeloid neoplasm with eosinophilia, complete hematological and cytogenetic remission was achieved at a daily dose of 20 mg and the patient continued on futibatinib, with evidence of hematologic and cytogenetic remission after >18 months of therapy [68].

A study evaluating efficacy and safety of pemigatinib in subjects with myeloid/lymphoid neoplasms with *FGFR1* rearrangement is currently recruiting (clinicaltrials.gov identifier: NCT03011372). According to interim data from 14 patients, pemigatinib showed promising efficacy with 80% of major cytogenetic response, including six cases with complete and two with partial cytogenetic response [69].

2.1.3.2. FLT3- and ABL1-rearranged myeloid/lymphoid neoplasms with eosinophilia. Small molecules targeting TKIs have also been evaluated in *FLT3*-mutated myeloid/lymphoid neoplasms with eosinophilia.

In a small series of two cases of *ETV6-FLT3*-positive myeloid/lymphoid neoplasms with eosinophilia, one patient achieved a complete hematological and cytogenetic response after 3 months of sunitinib therapy and a subsequent blast phase responded briefly to sorafenib being followed by a further relapse. The second case, heavily pretreated according to the initial diagnosis of T-cell lymphoblastic lymphoma, received sunitinib achieving rapid clearance of HE, but died from sunitinib-induced pancytopenia [70].

A further case of *ETV6-FLT3*-positive myeloid neoplasm with eosinophilia was treated upfront with sorafenib and obtained a partial cytogenetic response after 1.5 months of therapy. Consolidation with ASCT was then performed [71].

Recently, a series of 12 patients with *FLT3* rearrangement and eosinophilia associated with CEL, NOS, T-lymphoblastic leukemia/lymphoma, myeloid sarcoma, chronic myelomonocytic leukemia or myelodysplastic syndrome have been reported. Eleven patients received disease-based chemotherapy or hypomethylating agents, five proceeded to ASCT, and three received FLT3 inhibitors. Of the latter, one was treated with sorafenib alone, achieving CHR and partial cytogenetic response before ASCT. The remaining two cases received chemotherapy associated in one subject with sorafenib and sunitinib achieving complete response and proceeding to ASCT and in the other with gilteritinib obtaining a CCyR [72].

Sorafenib was administered in two other cases with eosinophilia and *FLT3* rearrangement, the first associated with CEL, NOS, and T-cell lymphoblastic leukemia/lymphoma and the second with myeloid sarcoma. The first patient was initially treated with intensive chemotherapy and subsequently received sorafenib with clinical improvement; however, he died from pneumonia while in persistent residual disease. The second subject was instead treated with local radiation and systemic chemotherapy including sorafenib and was still alive at the time of the survey [73].

Prolonged responses to TKIs have been reported in patients with *ETV6-ABL1* fusion genes. A recent analysis of 18 patients with myeloid neoplasms associated with tyrosine kinase fusion genes also included

nine *ETV6-ABL1*-positive cases, six in chronic phase and three in blast phase, all with AEC $\geq 1.5 \times 10^9$/L. Durable CHR was achieved in four out of nine cases, one of five treated with imatinib, two out of three with nilotinib and one of one with dasatinib. Due to the lack of hematological and/or cytogenetic/molecular response, five cases treated with imatinib and one with nilotinib were switched to nilotinib or dasatinib. Five of these six patients achieved a CCyR or CMR, suggesting that nilotinib or dasatinib may be more effective than imatinib in *ETV6-ABL1*-positive patients [61].

2.2. Monoclonal antibodies

2.2.1. IL-5 directed therapy: mepolizumab, reslizumab, benralizumab

The activity as therapeutic agents in HES of anti-IL-5 monoclonal antibodies such as mepolizumab and reslizumab and anti-IL-5Rα such as benralizumab, was investigated on the basis of pivotal role of the IL-5 pathway for eosinophils differentiation, activation, and survival.

The crucial contribution of this cytokine in the pathogenetic mechanism of HES has also been suggested by animal models showing that while mice transplanted with *FIP1L1-PDGFRA*-transduced hematopoietic stem cells/progenitors develops a CML-like MPN, the co-expression of *FIP1L1-PDGFRA* with transgenic IL-5 overexpression by T cells induced PB striking eosinophilia and eosinophil tissue infiltration of the heart, lungs, kidneys, small intestine, liver, and spleen mimicking a HES-like disease [74].

2.2.1.1. Mepolizumab. Mepolizumab, a fully humanized monoclonal IgG antibody that binds and neutralizes IL-5 [75], has been approved by the FDA for the treatment of severe eosinophilic asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic granulomatosis with polyangiitis.

On September 2020, mepolizumab also obtained approval for HES. The potential role of mepolizumab for the treatment of the latter condition had already been suggested as early as 2003/2004 by preliminary data on small series of patients showing a reduction of PB AEC and CS-sparing activity [76,77].

The CS-sparing effect and safety of mepolizumab were therefore evaluated in a randomized, double-blind trial in CS-dependent HES patients without the *FIP1L1-PDGFRA* fusion gene and requiring prednisone monotherapy, 43 assigned to treatment with mepolizumab and 42 to placebo.

The primary endpoint of reducing the dose of prednisone to 10 mg or less per day for eight or more consecutive week was reached in 84% of subjects in the mepolizumab group compared with 43% in the placebo group. Additionally, mepolizumab was significantly more effective than placebo in stabilizing PB AEC at $<0.6 \times 10^9$/L for eight or more consecutive weeks (95% vs. 45% of cases, respectively). Interestingly, the likelihood of response was not predicted by pretreatment serum IL-5 levels. Serious adverse events (AEs) occurred in seven patients treated with mepolizumab and in five receiving placebo [78].

A subsequent open-label extension study confirmed that mepolizumab was well tolerated and effective as a long-term CS-sparing agent in *PDGFRA*-negative HES [79].

Since L-HES are characterized by a marked overproduction of IL-5 by dysregulated T cells, 13 L-HES cases were investigated in a subgroup analysis of the randomized mepolizumab trial [78] in order to assess whether CS tapering and eosinophil depletion were achieved to the same extent as patients with a normal T-cell profile. While mepolizumab CS-sparing activity remained similar, a lower proportion of L-HES cases maintained eosinophil levels below 0.6×10^9/L, possibly due to incomplete neutralization of IL-5 or other eosinophilopoietic factors produced by dysregulated T cells [80].

In a retrospective analysis, long-term clinical outcomes of high-dose mepolizumab were evaluated in 35 treatment-refractory HES patients with severe disease including 20 idiopathic, six overlap, six lymphocytic and three myeloid variants. At the dosage of 750 mg iv every 4 weeks, 20 subjects achieved a complete and seven a partial clinical response while eight did not respond. The idiopathic and overlap forms were the most responsive. Of the six cases of L-HES, two achieved a complete and two a partial response; none of the three *JAK2*-mutated myeloid cases was responsive. Peak eosinophilia, CS sensitivity, pulmonary involvement, HES clinical subtype and pretreatment serum IL-5 levels were correlated with mepolizumab response [81].

In a subsequent multicenter, double-blind, phase III trial 108 *FIP1L1-PDGFRA*-negative HES patients with two or more flares (defined as worsening of HES-related symptoms requiring therapy escalation, two or more courses of blinded CS rescue, early withdrawal from the study) within the previous 12 months and a screening PB AEC greater than or equal to 1.0×10^9/L, were randomized (1:1) to subcutaneous mepolizumab (300 mg) or placebo every four weeks for 32 weeks. The primary endpoint was the proportion of patients who experienced a flare during the 32-week study period.

Mepolizumab vs. placebo significantly reduced the onset of flares (28% vs. 53%) and lowered the risk of experiencing a first flare by 66% during the treatment period. Moreover, at week 32, subjects receiving mepolizumab had a 92% reduction in PB AEC from baseline compared with those receiving placebo. Both groups had a similar rate of AEs [82]. This study led to FDA approval of mepolizumab for idiopathic HES.

To further characterize safety and efficacy of mepolizumab, patients from both treatment arms (prior placebo, $n = 52$; prior mepolizumab, $n = 50$) of the aforementioned study [82] entered an open-label extension study to receive 4-weekly mepolizumab (300 mg subcutaneously) plus background therapy for 20 weeks. Primary endpoints were safety-based; other endpoints included flare rates and changes from baseline in mean daily oral CS dose and PB AEC. Extended mepolizumab treatment was associated with a positive benefit-risk profile and continued control of disease flares and PB AEC; furthermore, reductions in CS use were recorded [83].

According to two post hoc analyzes of the same phase III trial [82], mepolizumab reduced HES flares regardless of baseline PB AEC and IL-5 levels [84] as well as baseline therapy [85].

2.2.1.2. Reslizumab. Reslizumab, another humanized anti-IL-5 monoclonal antibody approved by the FDA in March 2016 as an add-on maintenance treatment for severe eosinophilic asthma, has been poorly evaluated in HES.

In a small series of four patients with HES refractory or intolerant to conventional therapies, in two cases a single dose of reslizumab resulted in a rapid drop in AEC to the normal range with marked improvement in symptoms. Response was not predicted by serum IL-5 levels or presence of the *FIP1L1-PDGFRA* rearrangement. Upon exacerbation of symptoms and eosinophilia, resuming treatment with monthly dosing led to decreased eosinophilia and symptomatic improvement, albeit to a lesser extent than after the initial dose [86].

In a case of CS-refractory HE with a *TET2* mutation suggestive of CEL, NOS, administration of reslizumab led to rapid and persistent AEC normalization [87].

2.2.1.3. Benralizumab. Benralizumab is a humanized anti-IL-5Rα monoclonal antibody. After binding to IL-5Rα, eosinophils become a target for destruction by NK cells through antibody-dependent cell-mediated cytotoxicity [88].

Benralizumab was approved by the FDA in November 2017 as an add-on maintenance therapy for patients with severe asthma who have an eosinophilic phenotype. FDA also granted Orphan Drug Designation for the treatment of HES to benralizumab in February 2019.

In the phase III SIROCCO trial, subjects with severe eosinophilic asthma in the benralizumab group had drastically reduced AECs by week 4 of treatment, remaining through week 48, while in the placebo cohort it was unchanged [89].

The randomized CALIMA study, which also involved patients with severe eosinophilic asthma, showed similar results on PB AECs over 56 weeks of therapy [90].

The phase III ZONDA trial demonstrated comparable findings in patients with severe CS-dependent asthma. Subjects treated with benralizumab showed a dramatic reduction in AEC at week 12 from treatment start and a median reduction in oral CS dosages of 75% vs. 25% in the placebo group [91].

In the context of a randomized, placebo-controlled phase II trial, benralizumab was also evaluated in 20 symptomatic patients with heterogeneous subtypes of heavily-pretreated *PDGFRA*-negative HES. The study had three sequential stages: a randomized, double-blind, placebo-controlled phase (12 weeks), an open-label phase (12 weeks), and an extension phase for cases responsive at week 24. In the randomized phase, the primary endpoint (i.e., at least a 50% reduction in AEC at week 12) was achieved in 90% of benralizumab-treated subjects vs. 30% of the placebo group. During the open-label phase, clinical and hematological responses were reported in 17/19 patients, remaining through week 48 in 14 cases. The two unresponsive patients had a diagnosis of *JAK2*-mutated primary myeloid HES, with a lack of response similar to that also reported with mepolizumab [81]. While all three relapsed patients had an aberrant clonal CD3−/CD4+ T-cell population, a further biologically similar case achieved a lasting clinical response [92].

A phase III placebo-controlled clinical trial (clinicaltrials.gov identifier: NCT04191304) is currently ongoing to further evaluate safety and efficacy of benralizumab in patients with HES.

2.2.2. Omalizumab

Omalizumab is an FDA-approved anti-IgE monoclonal antibody for the treatment of asthma and chronic idiopathic urticaria, which has also shown promising efficacy in HES.

Pooled data from five randomized trials in patients with allergic asthma demonstrated a significant reduction in PB AEC compared to placebo, although not as relevant and long-lasting as with anti-IL-5/IL-5Rα antibodies. Probably, omalizumab indirectly affects AECs by inhibiting the release of cytokines such as IL-4, IL-5 and IL-13, all of which are involved in recruitment and activation of eosinophils [93]. Finally, several studies have reported that a baseline AEC $\geq 0.3 \times 10^9$/L may represent a positive predictor for omalizumab efficacy in allergic asthma treatment [94,95].

2.2.3. Dupilumab

Dupilumab is a human monoclonal IgG4 antibody that recognizes the IL-4Rα subunit of the IL-4 and IL-13 receptors [96], which play an important role in type 2 immune responses, such as those in which allergens act as the main antigen drivers. Given the nature and possibilities of blocking a critical pathway of type 2 immune responses, indications for dupilumab are increasing. For example, the drug is being studied as a treatment for atopic dermatitis, allergic contact dermatitis, chronic pruritus, chronic hand eczema, chronic spontaneous, cholinergic, or cold-inducible urticaria, bullous pemphigoid, and alopecia areata [97]. In addition, it is being developed for the treatment of allergic bronchopulmonary aspergillosis, allergic rhinitis, chronic eosinophilic pneumonia, and other type 2 diseases that affect other organs (e.g., gastrointestinal disorders), with promising results in eosinophilic esophagitis [97,98].

As reported for most clinical trials, a transient and clinically insignificant increase in PB AEC was observed after treatment with dupilumab. Similarly, real-life practice has shown that these cases are actually quite frequent, especially in some conditions such as the treatment of atopic dermatitis [99]: as recently reported, HE seemed to have no clinical significance, without signs of organ damage documented in patients with HE at baseline or developing during treatment. Nevertheless, it should be emphasized that HE with systemic clinical manifestations can develop if treatment does not focus on appropriate control of PB AEC, as anti–IL-5/IL-5Rα and CS agents do [100,101]. These observations support the indication for dual therapy with anti–IL-5 agents and dupilumab in this clinical scenario [102].

2.2.4. Alemtuzumab

Alemtuzumab, a humanized anti-CD52 IgG1k monoclonal antibody originally developed for the treatment of chronic lymphocytic leukemia and other lymphoproliferative disorders, was also tested in HES for expression of CD52 antigen on the surface of eosinophils. First, alemtuzumab has been shown to normalize AEC, while improving clinical symptoms, in two cases of refractory idiopathic HES [103,104].

In a subsequent study of nine patients with idiopathic HES and three with CEL, NOS, treatment with alemtuzumab resulted in a CHR, defined as normalization of AEC for a median duration of 66 weeks, with resolution of disease-related symptoms, in 10 subjects, while two cases achieved at least a partial hematological remission. Patients with CHR who received alemtuzumab maintenance ($n = 5$) had a significantly longer time to progression than those under observation alone ($n = 5$). Eleven patients, including only one during maintenance, relapsed and five of the six cases who were re-treated achieved a second CHR. Regarding AEs, two patients suffered from cytomegalovirus reactivation, one zoster reactivation and one an orbital NHL, all due T-cell depletion induced by alemtuzumab, with consequent impairment of immune surveillance. Accordingly, due to its unfavorable safety profile, the use of alemtuzumab appears appropriate only in a rescue setting for refractory diseases [105].

3. Summary and future directions

The increasing amount of molecular knowledge underlying HES subtypes has led to a dramatic improvement in therapeutic options based on targeted agents. Although imatinib is robustly the drug of choice for the first-line treatment of *PDGFRA/B*-rearranged HES (albeit with a different dosage based on the specific abnormality), more data from clinical trials would help to better define maintenance strategies and, even more, clarify the minimum requirements necessary to safely discontinue treatment. Second-line therapies after imatinib failure and drugs targeting other mutations, such as *FGFR1* or *JAK2* among others, still represent an unmet medical need, with intensive chemotherapy followed by early ASCT still recommended for frontline treatment of these cases who may frequently present or progress to blast-phase disease. Monoclonal antibodies active on eosinophils, directly or indirectly, have further expanded HES treatment strategies. Although anti-IL-5/IL-5Rα antibodies can produce a significant rate of hematological response and clinical improvement, some questions still need to be clarified such as, for example, the most appropriate dose of mepolizumab for CS-refractory HES, long-term safety of eosinophil depletion, rather than normalization, induced by benralizumab, or the transient increase in PB AEC observed after treatment with dupilumab. Furthermore, it should also be admitted that precise criteria allowing physicians to choose the best monoclonal antibody for each patient are still lacking.

Practice points

- Hypereosinophilic syndromes include a wide range of disorders characterized by hypereosinophilia, which can be associated with life-threatening organ damage.
- The 2016 WHO revision approved a semi-molecular classification scheme for the disease subtypes, including the following main categories: myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA/B*, or *FGFR1* or with *PCM1-JAK2*; myeloproliferative neoplasm subtype, CEL, NOS; and idiopathic HES.
- Primary HES diagnostic work-up is based on a combination of PB and BM morphological assessment, blood tests, standard cytogenetic techniques, FISH, flow cytometry, and molecular analysis to detect

histopathological or molecular evidence of an acute or chronic myeloid or lymphoid neoplasm.

- Therapy should be directed at the underlying HES etiology, with the aim of mitigating eosinophil-mediated organ damage. Hypereosinophilia must be treated promptly and aggressively to reduce potential morbidity and mortality whenever organ damage is detected.
- Imatinib is the only TKI approved by FDA for HES therapy as it represents the drug of choice for myeloid neoplasms with eosinophilia and *PDGFRA/B* rearrangement.
- In recent years, some FDA-approved JAK inhibitors have been tested in HES, especially in those cases associated with gain-of-function mutations involved in the JAK/STAT signaling pathway, with promising results, especially in *PCM1-JAK2*-positive cases.
- Anti-IL-5/IL-5Rα antibodies, including mepolizumab, reslizumab, and benralizumab, were tested in HES based on the role of cytokines as a differentiation, activation, and survival factor for eosinophils, showing great potential to be efficacious in this setting.

Research agenda

- The acquisition of new molecular information will provide data to make an increasingly precise diagnosis of these rare entities, in order to drastically reduce the number of so-called idiopathic forms.
- Several novel tyrosine kinase inhibitors and monoclonal antibodies have been shown to effectively reduce the number of eosinophils in HES, with little or no adverse events.
- Consequently, each case of HES should be followed up regularly in hematological centers with clear experience in this context. As with other rare diseases, it is crucial to include these patients in clinical trials whenever possible.

Authors' contributions

AI and DC wrote the paper and gave their final approval.

Disclosures

The authors declare they have no potential conflicts of interest.

Acknowledgments

This study was partially funded by Italian Ministry of Health - Current research IRCCS.

References

[1] Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J Allergy Clin Immunol 2012;130:607–12.
[2] Rothenberg ME. Eosinophilia. N Engl J Med 1998;338:1592–600.
[3] Tefferi A, Patnaik MM, Pardanani A. Eosinophilia: secondary, clonal and idiopathic. Br J Haematol 2006;133:468–92.
[4] Ruan GJ, Smith CJ, Day C, et al. A population-based study of chronic eosinophilic leukemia-not otherwise specified in the United States. Am J Hematol 2020;95:E257–60.
[5] Jin JJ, Butterfield JH, Weiler CR. Hematologic malignancies identified in patients with hypereosinophilia and hypereosinophilic syndromes. J Allergy Clin Immunol Pract 2015;3:920–5.
[6] Andersen CL, Siersma VD, Hasselbalch HC, et al. Eosinophilia in routine blood samples and the subsequent risk of hematological malignancies and death. Am J Hematol 2013;88:843–7.
[7] Wang SA. The diagnostic work-up of hypereosinophilia. Pathobiology 2019;86:39–52.
[8] Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391–405.
[9] Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703–19.
[10] Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemia: integrating morphological, clinical, and genomic data. Blood 2022;140:1200–28 [Online ahead of print].
[11] Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification and management. Am J Hematol 2022;97:129–48.
[12] Iurlo A, Cattaneo D, Gianelli U. Hypereosinophilic syndromes in the precision medicine era: clinical, molecular aspects and therapeutic approaches (targeted therapies). Expert Rev Hematol 2019;12:1077–88.
[13] Gleich GJ, Leiferman KM, Pardanani A, Tefferi A, Butterfield JH. Treatment of hypereosinophilic syndrome with imatinib mesilate. Lancet 2002;359:1577–8.
[14] Ault P, Cortes J, Koller C, Kaled ES, Kantarjian H. Response of idiopathic hypereosinophilic syndrome to treatment with imatinib mesylate. Leuk Res 2002;26:881–4.
[15] Ogbogu PU, Bochner BS, Butterfield JH, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. J Allergy Clin Immunol 2009;124:1319–25.
[16] Helbig G. Imatinib for the treatment of hypereosinophilic syndromes. Expert Rev Clin Immunol 2018;14:163–70.
[17] Stella S, Massimino M, Manzella L, et al. Molecular pathogenesis and treatment perspectives for hypereosinophilia and hypereosinophilic syndromes. Int J Mol Sci 2021;22:486.
[18] Jovanovic JV, Score J, Waghorn K, et al. Low-dose imatinib mesylate leads to rapid induction of major molecular responses and achievement of complete molecular remission in FIP1L1-PDGFRA-positive chronic eosinophilic leukemia. Blood 2007;109:4635–40.
[19] Klion AD, Robyn J, Akin C, et al. Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. Blood 2004;103:473–8.
[20] Baccarani M, Cilloni D, Rondoni M, et al. The efficacy of imatinib mesylate in patients with FIP1L1-PDGFRa-positive hypereosinophilic syndrome. Results of a multicenter prospective study. Haematologica 2007;92:1173–9.
[21] Metzgeroth G, Walz C, Erben P, et al. Safety and efficacy of imatinib in chronic eosinophilic leukaemia and hypereosinophilic syndrome: a phase-II study. Br J Haematol 2008;143:707–15.
[22] Legrand F, Renneville A, MacIntyre E, et al. The spectrum of FIP1L1-PDGFRA-associated chronic eosinophilic leukemia: new insights based on a survey of 44 cases. Medicine (Baltimore) 2013;92:e1–9.
[23] Helbig G, Stella-Hołowiecka B, Majewski M, et al. A single weekly dose of imatinib is sufficient to induce and maintain remission of chronic eosinophilic leukaemia in FIP1L1-PDGFRA expressing patients. Br J Haematol 2008;141:200–4.
[24] Helbig G, Moskwa A, Hus M, et al. Durable remission after treatment with very low doses of imatinib for FIP1L1-PDGFRα-positive chronic eosinophilic leukaemia. Cancer Chemother Pharmacol 2011;67:967–9.
[25] Pardanani A, D'Souza A, Knudson RA, Hanson CA, Ketterling RP, Tefferi A. Long-term follow-up of FIP1L1-PDGFRA-mutated patients with eosinophilia: survival and clinical outcome. Leukemia 2012;26:2439–41.
[26] Qu SQ, Qin TJ, Xu ZF, et al. Long-term outcomes of imatinib in patients with FIP1L1/PDGFRA associated chronic eosinophilic leukemia: experience of a single center in China. Oncotarget 2016;7:33229–36.
[27] Helbig G, Lewandowski K, Świderska A, Rodzaj M, Seferyńska I, Gajkowska-Kulik J. Exquisite response to imatinib mesylate in FIP1L1-PDGFRA-mutated hypereosinophilic syndrome: a 12-year experience of the Polish Hypereosinophilic Syndrome Study Group. Pol Arch Intern Med 2020;130:255–7.
[28] Klion AD, Robyn J, Maric I, et al. Relapse following discontinuation of imatinib mesylate therapy for FIP1L1/PDGFRA-positive chronic eosinophilic leukemia: implications for optimal dosing. Blood 2007;110:3552–6.
[29] Helbig G, Soja A, Świderska A, Hus M, Kyrcz-Krzemien S. Imatinib discontinuation for hypereosinophilic syndrome harboring the FIP1L1-PDGFRA transcript. Leuk Lymphoma 2016;57:708–10.
[30] Metzgeroth G, Schwaab J, Naumann N, et al. Treatment-free remission in FIP1L1-PDGFRA–positive myeloid/lymphoid neoplasms with eosinophilia after imatinib discontinuation. Blood Adv 2020;4:440–3.
[31] Rohmer J, Couteau-Chardon A, Trichereau J, et al. Epidemiology, clinical picture and long-term outcomes of FIP1L1-PDGFRA-positive myeloid neoplasm with eosinophilia: data from 151 patients. Am J Hematol 2020;95:1314–23.
[32] Metzgeroth G, Erben P, Martin H, et al. Limited clinical activity of nilotinib and sorafenib in FIP1L1-PDGFRA positive chronic eosinophilic leukemia with imatinib-resistant T674I mutation. Leukemia 2012;26:162–4.
[33] von Bubnoff N, Gorantla SP, Engh RA, et al. The low frequency of clinical resistance to PDGFR inhibitors in myeloid neoplasms with abnormalities of PDGFRA might be related to the limited repertoire of possible PDGFRA kinase domain mutations in vitro. Oncogene 2011;30:933–43.
[34] Lierman E, Cools J. Recent breakthroughs in the understanding and management of chronic eosinophilic leukemia. Expert Rev Anticancer Ther 2009;9:1295–304.
[35] Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med 2003;348:1201–14.
[36] Bradeen HA, Eide CA, O'Hare T, et al. Comparison of imatinib mesylate, dasatinib (BMS-354825), and nilotinib (AMN107) in an N-ethyl-N-nitrosourea (ENU)-based mutagenesis screen: high efficacy of drug combinations. Blood 2006;108:2332–8.
[37] Lierman E, Michaux L, Beullens E, et al. FIP1L1-PDGFRalpha D842V, a novel panresistant mutant, emerging after treatment of FIP1L1-PDGFRalpha T674I eosinophilic leukemia with single agent sorafenib. Leukemia 2009;23:845–51.

[38] Simon D, Salemi S, Yousefi S, Simon HU. Primary resistance to imatinib in Fip1-like 1-platelet-derived growth factor receptor alpha-positive eosinophilic leukemia. J Allergy Clin Immunol 2008;121:1054–6.
[39] Gorantla SP, Zirlik K, Reiter A, et al. F604S exchange in FIP1L1-PDGFRA enhances FIP1L1-PDGFRA protein stability via SHP-2 and SRC: a novel mode of kinase inhibitor resistance. Leukemia 2015;29:1763–70.
[40] Metzgeroth G, Walz C, Score J, et al. Recurrent finding of the FIP1L1-PDGFRA fusion gene in eosinophilia-associated acute myeloid leukemia and lymphoblastic T-cell lymphoma. Leukemia 2007;21:1183–8.
[41] Metzgeroth G, Schwaab J, Gosenca D, et al. Long-term follow-up of treatment with imatinib in eosinophilia-associated myeloid/lymphoid neoplasms with PDGFR rearrangements in blast phase. Leukemia 2013;27:2254–6.
[42] Apperley JF, Gardembas M, Melo JV, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. N Engl J Med 2002;347:481–7.
[43] David M, Cross NC, Burgstaller S, et al. Durable responses to imatinib in patients with PDGFRB fusion gene-positive and BCR-ABL-negative chronic myeloproliferative disorders. Blood 2007;109:61–4.
[44] Cheah CY, Burbury K, Apperley JF, et al. Patients with myeloid malignancies bearing PDGFRB fusion genes achieve durable long-term remissions with imatinib. Blood 2014;123:3574–7.
[45] Jawhar M, Naumann N, Schwaab J, et al. Imatinib in myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRB in chronic or blast phase. Ann Hematol 2017;96:1463–70.
[46] Naumann N, Schwaab J, Metzgeroth G, et al. Fusion of PDGFRB to MPRIP, CPSF6, and GOLGB1 in three patients with eosinophilia-associated myeloproliferative neoplasms. Genes Chromosomes Cancer 2015;54:762–70.
[47] Jain N, Cortes J, Quintas-Cardama A, et al. Imatinib has limited therapeutic activity for hypereosinophilic syndrome patients with unknown or negative PDGFRa mutation status. Leuk Res 2009;33:837–9.
[48] Helbig G. Imatinib mesylate for unmutated hypereosinophilic syndromes: does it work? Eur J Intern Med 2016;32:e19–20.
[49] Khoury P, Desmond R, Pabon A, et al. Clinical features predict responsiveness to imatinib in platelet-derived growth factor receptor-alpha-negative hypereosinophilic syndrome. Allergy 2016;71:803–10.
[50] Iurlo A, Fracchiolla NS, Ferla V, et al. Successful treatment with imatinib in a patient with chronic eosinophilic leukemia not otherwise specified. J Clin Oncol 2014;32:e37–9.
[51] Iurlo A, Gianelli U, Beghini A, et al. Identification of kit(M541L) somatic mutation in chronic eosinophilic leukemia, not otherwise specified and its implication in low-dose imatinib response. Oncotarget 2014;5:4665–70.
[52] Pardanani A, Reeder T, Porrata LF, et al. Imatinib therapy for hypereosinophilic syndrome and other eosinophilic disorders. Blood 2003;101:3391–7.
[53] Pitini V, Arrigo C, Azzarello D, et al. Serum concentration of cardiac Troponin T in patients with hypereosinophilic syndrome treated with imatinib is predictive of adverse outcomes. Blood 2003;102:3456–7.
[54] Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol 2018;15:234–48.
[55] Del Bel KL, Ragotte RJ, Saferali A, et al. JAK1 gain-of-function causes an autosomal dominant immune dysregulatory and hypereosinophilic syndrome. J Allergy Clin Immunol 2017;139:2016–20.
[56] Lierman E, Selleslag D, Smits S, Billiet J, Vandenberghe P. Ruxolitinib inhibits transforming JAK2 fusion proteins in vitro and induces complete cytogenetic remission in t(8;9)(p22;p24)/PCM1-JAK2-positive chronic eosinophilic leukemia. Blood 2012;120:1529–31.
[57] Schwaab J, Knut M, Haferlach C, et al. Limited duration of complete remission on ruxolitinib in myeloid neoplasms with PCM1-JAK2 and BCR-JAK2 fusion genes. Ann Hematol 2015;94:233–8.
[58] Rumi E, Milosevic JD, Selleslag D, et al. Efficacy of ruxolitinib in myeloid neoplasms with PCM1-JAK2 fusion gene. Ann Hematol 2015;94:1927–8.
[59] Rumi E, Milosevic JD, Casetti I, et al. Efficacy of ruxolitinib in chronic eosinophilic leukemia associated with a PCM1-JAK2 fusion gene. J Clin Oncol 2013;31:e269–71.
[60] King B, Lee AI, Choi J. Treatment of hypereosinophilic syndrome with cutaneous involvement with the JAK inhibitors tofacitinib and ruxolitinib. J Invest Dermatol 2017;137:951–4.
[61] Schwaab J, Naumann N, Luebke J, et al. Response to tyrosine kinase inhibitors in myeloid neoplasms associated with PCM1-JAK2, BCR-JAK2 and ETV6-ABL1 fusion genes. Am J Hematol 2020;95:824–33.
[62] Chen JA, Hou Y, Roskin KM, et al. Lymphoid blast transformation in an MPN with BCR-JAK2 treated with ruxolitinib: putative mechanisms of resistance. Blood Adv 2021;5:3492–6.
[63] Chase A, Bryant C, Score J, Cross NCP. Ponatinib as targeted therapy for FGFR1 fusions associated with the 8p11 myeloproliferative syndrome. Haematologica 2013;98:103–6.
[64] Ren M, Qin H, Ren R, Cowell JK. Ponatinib suppresses the development of myeloid and lymphoid malignancies associated with FGFR1 abnormalities. Leukemia 2013;27:32–40.
[65] Kreil S, Ades L, Bommer M, et al. Limited efficacy of ponatinib in myeloproliferative neoplasms associated with FGFR1 fusion genes. Blood 2015;126:2812 (abstract).
[66] Chen J, Deangelo DJ, Kutok JL, et al. PKC412 inhibits the zinc finger 198-fibroblast growth factor receptor 1 fusion tyrosine kinase and is active in treatment of stem cell myeloproliferative disorder. Proc Natl Acad Sci U S A 2004;101:14479–84.
[67] Strati P, Tang G, Duose DY, et al. Myeloid/lymphoid neoplasms with FGFR1 rearrangement. Leuk Lymphoma 2018;59:1672–6.
[68] Kasbekar M, Nardi V, Dal Cin P, et al. Targeted FGFR inhibition results in a durable remission in an FGFR1-driven myeloid neoplasm with eosinophilia. Blood Adv 2020;4:3136–40.
[69] Verstovsek S, Vannucchi AM, Rambaldi A, et al. Interim results from Fight-203, a Phase 2, open-label, multicenter study evaluating the efficacy and safety of pemigatinib (INCB054828) in patients with myeloid/lymphoid neoplasms with rearrangement of fibroblast growth factor receptor (FGFR1). Blood 2018;132:690 (abstract).
[70] Walz C, Erben P, Ritter M, et al. Response of ETV6-FLT3-positive myeloid/lymphoid neoplasm with eosinophilia to inhibitors of FMS-like tyrosine kinase 3. Blood 2011;118:2239–42.
[71] Falchi L, Mehrotra M, Newberry KJ, et al. ETV6-FLT3 fusion gene-positive, eosinophilia- associated myeloproliferative neoplasm successfully treated with sorafenib and allogeneic stem cell transplant. Leukemia 2014;28:2090–2.
[72] Tang G, Tam W, Short NJ, et al. Myeloid/lymphoid neoplasms with FLT3 rearrangement. Mod Pathol 2021;34:1673–85.
[73] Shao H, Wang W, Song J, et al. Myeloid/lymphoid neoplasms with eosinophilia and FLT3 rearrangement. Leuk Res 2020;99:106460.
[74] Yamada Y, Rothenberg ME, Lee AW, et al. The FIP1L1-PDGFRA fusion gene cooperates with IL-5 to induce murine hypereosinophilic syndrome (HES)/chronic eosinophilic leukemia (CEL)-like disease. Blood 2006;107:4071–9.
[75] Pavord ID, Bel EH, Bourdin A, et al. From DREAM to REALITI-A and beyond: Mepolizumab for the treatment of eosinophil-driven diseases. Allergy 2022;77:778–97.
[76] Garrett JK, Jameson SC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. J Allergy Clin Immunol 2004;113:115–9.
[77] Plötz SG, Simon HU, Darsow U, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. N Engl J Med 2003;349:2334–9.
[78] Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. N Engl J Med 2008;358:1215–28.
[79] Roufosse FE, Kahn JE, Gleich GJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. J Allergy Clin Immunol 2013;131:461–7.
[80] Roufosse F, de Lavareille A, Schandene L, et al. Mepolizumab as a corticosteroid-sparing agent in lymphocytic variant hypereosinophilic syndrome. J Allergy Clin Immunol 2010;126. 828–35.e3.
[81] Kuang FL, Fay MP, Ware J, et al. Long-term clinical outcomes of high-dose mepolizumab treatment for hypereosinophilic syndrome. J Allergy Clin Immunol Pract 2018;6. 1518–27.e5.
[82] Roufosse F, Kahn JE, Rothenberg ME, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: a phase III, randomized, placebo-controlled trial. J Allergy Clin Immunol 2020;146:1397–405.
[83] Gleich GJ, Roufosse F, Chupp G, et al. Safety and efficacy of mepolizumab in hypereosinophilic syndrome: an open-label extension study. J Allergy Clin Immunol Pract 2021;9. 4431–40.e1.
[84] Rothenberg ME, Roufosse F, Faguer S, et al. Mepolizumab reduces hypereosinophilic syndrome flares irrespective of blood eosinophil count and interleukin-5. J Allergy Clin Immunol Pract 2022;10:2367–2374.e3.
[85] Reiter A, Lefevre G, Cid MC, et al. Association between baseline therapy and flare reduction in mepolizumab-treated patients with hypereosinophilic syndrome. Front Immunol 2022;13:840974.
[86] Klion AD, Law MA, Noel P, Kim YJ, Haverty TP, Nutman TB. Safety and efficacy of the monoclonal anti-interleukin-5 antibody SCH55700 in the treatment of patients with hypereosinophilic syndrome. Blood 2004;103:2939–41.
[87] Coffey K, Fajt ML, Acho M, Gladwin M, Petrov AA. Successful treatment of corticosteroid-refractory hypereosinophilia with reslizumab. J Investig Allergol Clin Immunol 2019;29:241–2.
[88] Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immunol 2010;125. 1344–53.e2.
[89] Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388:2115–27.
[90] FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388:2128–41.
[91] Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 2017;376:2448–58.
[92] Kuang FL, Legrand F, Makiya M, et al. Benralizumab for PDGFRA-negative hypereosinophilic syndrome. N Engl J Med 2019;380:1336–46.
[93] Massanari M, Holgate ST, Busse WW, Jimenez P, Kianifard F, Zeldin R. Effect of omalizumab on peripheral blood eosinophilia in allergic asthma. Respir Med 2010;104:188–96.
[94] Busse W, Spector S, Rosen K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. J Allergy Clin Immunol 2013;132. 485–6.e11.
[95] Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 2013;187:804–11.

[96] Paton DM. Dupilumab: human monoclonal antibody against IL-4Rα for moderate to severe atopic dermatitis. Drugs Today (Barc) 2017;53:477–87.
[97] Muñoz-Bellido JJ, Moreno E, Dávila I. Dupilumab: a review of present indications and off-label uses. J Investig Allergol Clin Immunol 2022;32:97–115.
[98] Matsunaga K, Katoh N, Fujieda S, Izuhara K, Oishi K. Dupilumab: basic aspects and applications to allergic diseases. Allergol Int 2020;69:187–96.
[99] Ferrucci S, Angileri L, Tavecchio S, et al. Elevation of peripheral blood eosinophils during dupilumab treatment for atopic dermatitis is associated with baseline comorbidities and development of facial redness dermatitis and ocular surface disease. J Dermatolog Treat 2022 Mar 9:1–6 [Online ahead of print].
[100] Eger K, Pet L, Weersink EJM, Bel EH. Complications of switching from anti-IL-5 or anti-IL-5R to dupilumab in corticosteroid-dependent severe asthma. J Allergy Clin Immunol Pract 2021;9:2913–5.
[101] Briegel I, Felicio-Briegel A, Mertsch P, Kneidinger N, Haubner F, Milger K. Hypereosinophilia with systemic manifestations under dupilumab and possibility of dual benralizumab and dupilumab therapy in patients with asthma and CRSwNP. J Allergy Clin Immunol Pract 2021;9:4477–9.
[102] Olaguibel JM, Sastre J, Rodríguez JM, Del Pozo V. Eosinophilia induced by blocking the IL-4/IL-13 pathway: potential mechanisms and clinical outcomes. J Investig Allergol Clin Immunol 2022;32:165–80.
[103] Pitini V, Teti D, Arrigo C, Righi M. Alemtuzumab therapy for refractory idiopathic hypereosinophilic syndrome with abnormal T cells: a case report. Br J Haematol 2004;127:477.
[104] Wagner LA, Speckart S, Cutter B, Gleich GJ. Treatment of FIP1L1/PDGFRA-negative hypereosinophilic syndrome with alemtuzumab, an anti-CD52 antibody. J Allergy Clin Immunol 2009;123:1407–8.
[105] Strati P, Cortes J, Faderl S, Kantarjian H, Verstovsek S. Long-term follow-up of patients with hypereosinophilic syndrome treated with Alemtuzumab, an anti-CD52 antibody. Clin Lymphoma Myeloma Leuk 2013;13:287–91.