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REVIEW

Novel therapies for hypereosinophilic syndromes

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ABSTRACT

Background: Conventional therapies (corticosteroids, cytotoxic agents or interferon-α) or newer compounds such imatinib are used specifically in subsets of hypereosinophilic syndromes (HES). However other therapies are still needed in this condition.
Objective: To review the novel therapies for HES discussing their advantages and shortcomings.
Methods and Results: Preclinical and clinical data on novel tyrosine kinase inhibitors, anti-IL-5 antibodies or anti-CD52 antibodies (alemtuzumab) are analysed. The former might represent appropriate options in case of imatinib resistance; the efficacy of anti-IL-5 monoclonal antibodies therapy is limited by the occurrence of rebound eosinophilia and alemtuzumab might be a promising anti-eosinophil therapy for all HES subsets.
Conclusion: Some of the novel therapies might become appropriate therapeutic options for HES.

KEYWORDS

Hypereosinophilic syndromes, tyrosine kinase inhibitors, anti-IL-5 monoclonal antibodies, alemtuzumab

INTRODUCTION

Hypereosinophilic syndromes (HES), along with systemic mastocytosis and chronic myelomonocytic leukaemia, belong to the group of atypical chronic myeloproliferative disorders.[1]
HES were initially defined with Chusid's criteria represented by blood eosinophilia >1500/mm^3 persisting for at least six consecutive months, exclusion of causes of secondary eosinophilia (i.e. allergy, parasitic infections, etc) and presence of end-organ impairment or dysfunction related to hypereosinophilia.[2]
In HES skin, heart, neurological and lung involvement were commonly reported in addition to cardiac manifestations, which have the highest lethal potential.[3]
Subsequently, however, based on identification of various genetic abnormalities several subtypes of HES were characterised: myeloproliferative, lymphoproliferative, autoimmune and familial.[4]
However, based on the current World Health Organisation (WHO) classification, three major subsets of previously termed HES are defined: patients with clonal eosinophilia (chronic eosinophilic leukaemia) caused by FIP1L1-PDGFRA fusion gene, patients with clonal IL-5/Th2 lymphoctyes mediated hypereosinophilia defined as 'lymphoproliferative' HES and finally patients with no evidence of clonal hypereosinophilia labelled as having 'idiopathic/myeloproliferative' HES.[5]
Such reclassification is important in order to reshape, in a more targeted fashion, the therapeutic approach according to the presence or absence of clonal proliferation and to pathogenic mechanisms of eosinophil clonality: the subset with chronic eosinophilic leukaemia would best benefit from tyrosine kinase inhibitors, lymphoproliferative subsets of anti-IL-5 antibodies and corticosteroids, whereas for the 'idiopathic' subset conventional therapy including corticosteroids, cytotoxic agents or bone marrow transplantation may still be appropriate as first-line therapies.
This paper reviews the existing therapeutic methods for all HES subsets focusing on the novel therapies represented by tyrosine kinases, anti-IL-5 or anti-CD52 antibodies and discusses the rationale for their use based on available preclinical and clinical data.

CURRENT THERAPIES FOR HES

The existing therapies which can be used in various forms of HES are represented by the conventional therapies and by the tyrosine kinase inhibitor imatinib mesylate (IM). The identification of various HES subsets accordingly led to a revision of the therapeutic recommendations and novel specific therapies such as IM replaced, for example, corticosteroids in HES/CEL subsets.

Conventional therapies for HES

Conventional therapies include corticosteroids, cytotoxic agents, interferon-α or bone marrow transplantation: some of these options, such as corticosteroids and cytotoxic agents, were previously more widely used in all HES subsets in general but based on current knowledge of underlying pathogenic mechanisms they are not recommended as first-line therapy in all HES subsets.

Corticosteroids were initially the mainstay of HES treatment and are currently recommended as first-line therapy in FIP1L1-PDGFRA-negative HES subsets.[6] However, in such patients disease relapse has been reported when attempting to taper the corticosteroid dose and on the other hand the side effects associated with their long-term use, such as cardiovascular abnormalities, gastrointestinal disorders, myopathy or diabetes, may challenge their current therapeutic position and have prompted evaluation of other potential treatments.

Cytotoxic agents have been used in HES therapy based on extrapolation of their efficacy in other myeloproliferative disorders: hydroxyurea was most commonly reported to be used previously as HES therapy but the latency of its therapeutic effect on eosinophil count reduction and the potential haematological or gastrointestinal adverse events which would aggravate the symptoms of HES, are limiting factors for its wider use.[4] Currently they are indicted in HES subsets with corticosteroid resistance or when steroid tapering is necessary.[6] Other cytotoxic agents for which there are isolated reports of improvement in HES disease outcome are vincristine, cytarabine 2-chlorodeoxyadenosine and etoposide.[7]

Interferon-alpha is an immunomodulator which was found to reduce Th2-mediated IL-5 production, synthesis of GM-CSF and release of eosinophil-specific neurotoxin and eosinophil cationic protein and indirectly inhibited eosinophil differentiation.[8-11]

It is recommended for use in HES patients with organ damage and corticosteroids/cytotoxic treatment failure.[9,12-14] The interferon-alpha/hydroxyurea combination has been shown to increase the clinical efficacy.[15]

Allogeneic bone marrow transplantation has also been reported to be a potentially curative therapy. It is recommended to be used as an ultimate therapeutic measure in case of therapeutic refractoriness or intolerance to available therapies or in case of multiple severe organ impairment, but is associated with major morbidity and even mortality.[16,17]

Tyrosine kinase inhibitors: imatinib mesylate

FIP1L1-PDGFRA oncogene is generated by a deletion in chromosome 4q12 and results in the development of fusion protein (FIP1L1-PDGFRA) with tyrosine kinase activities and was detected in the HES subset currently defined as CEL emerging rapidly as a therapeutic target for imatinib.[18] FIP1L1-PDGFRA oncogene occurs with a variable frequency predominantly in males, the endomyocardial fibrosis and mucosal ulceration were reported to occur more frequently in this subset, tryptase and B12 levels were found to be elevated, IgE levels are normal and thrombocytopenia, anaemia or myelofibrosis are other features of this disease phenotype.[6,7]

Imatinib mesylate (IM) is an aminopyrimidine which was previously found to block the Bcr-Abl tyrosine kinase, in the Philadelphia chromosome of chronic myeloid leukaemia. IM was demonstrated to exert inhibit tyrosine kinases such as platelet-derived growth factor receptor (PDGFR) or KIT, blocking their signalling pathways in Bcr-Abl negative disorders such as HES, systemic mastocytosis or gastrointestinal stromal tumours.[1,19,20]

Initial reports on clinical efficacy of IM came from isolated cases and then from case series: IM therapy was tentatively used for the first time in a HES patient previously treated with high doses of corticosteroids, hydroxyurea and INF-α and with a large eosinophil count in an attempt to reduce the doses of these medications: imatinib 100 mg/day resulted in a complete clearance of peripheral eosinophils after 35 days of therapy.[21] In a patient with multiple organ involvement and corticosteroid and cytotoxic agents refractoriness 14 days of IM therapy resulted in a complete haematological response (0% eosinophils in peripheral blood) and symptoms significant improvement.[22]

Subsequent case series reported complete haematological remissions in HES patients mostly with failure to respond to prior conventional therapies: such patients were reported to receive IM dosages ranging from 100 to 400 mg/day and both complete haematological response and duration of the therapeutic effects were found to vary.[23,24] In a particular study assessing the efficacy of IM in 11 HES patients, the complete remission was achieved within a median period of four weeks in ten out of 11 patients with IM doses within the same range as mentioned before, and the therapeutic effect was reported to persist for at least three months in nine out of 11 patients.[18] The most important findings of this study, however, were the identification of fusion gene FIP1L1-PDGFRA as the therapeutic target of imatinib therapy in five of the nine patients with long-standing

complete haematological response and the detection of a mutation in the fusion gene responsible for development of imatinib resistance.[18]

Overall in FIP1L1-PDGFRA positive patients with HES/CEL IM induced complete haematological remission (normalised white blood cell count and differential mainly eosinophil count), decreased bone marrow clonal cellularity and myelofibrosis and resulted in molecular remission as well.[1,18,25-31]

In FIP1L1/PDGFRA negative patients, however, IM therapy was not reported to have such spectacular effects as in the positive phenotype: in fact the efficacy was variable and both and besides reports of complete responses partial and non-response have been reported.[1,18,28,30]

Poor or absent therapeutic response to IM in FIP1L1/PDGFRA positive HES patients was a surprising although sporadic finding and was identified to be due to 'acquired' imatinib resistance which had also been detected previously in chronic myeloid leukaemia patients. Several mutations in the fusion gene are hypothesised to be responsible for imatinib resistance in HES and FIP1L1-PDGFRA T674I mutant is the only one currently documented clinically and used in preclinical studies to test alternative tyrosine kinase inhibitors such as nilotinib or sorafenib.[7]

NOVEL THERAPIES IN HES

Several therapies are currently under investigation as potential HES therapies: compounds such as newer tyrosine kinases are evaluated as alternative options in case of imatinib resistance in the HES/CEL subset, anti-IL-5 antibodies are being investigated for lymphoproliferative HES phenotype whereas anti-CD52 antibodies, given their eosinophil inhibitory potential, are being assessed for all HES subsets with therapeutic refractoriness.

Nilotinib

Nilotinib (AMN107) is another aminopyrimidine derivative sharing with imatinib many structural features as well as the potential of blocking kinases such as PDGFR, KIT or Bcr-Abl (breakpoint cluster region-abelson).[32] Unlike imatinib which blocks PDGFR activity to a greater extent, nilotinib exhibits a more potent inhibition on Bcr-Abl, and is able to act effectively, also on PDGFRA T674I mutated kinase which was identified to be associated with imatinib resistance in HES patients.[18,33] When tested *in vitro* on an EOL-1 cell line exhibiting FIP1L1-PDGFRA fusion kinase, nilotinib was found to exert a similar inhibitory effect to imatinib.[34] Nilotinib was also demonstrated to inhibit FIP1L1-PDGFRA activity in a Ba/F3 cell line and was also found to interfere with the development of myeloproliferative disorder induced by FIP1L1-PDGFRA in a mice model of bone marrow transplantation.[35] When tested clinically in a phase II study performed in 11 HES patients receiving nilotinib 400 mg twice daily, the complete remission was achieved in only one patient whereas in five others it stabilised the disease and three patients exhibited disease progression.[36]

Sorafenib

Sorafenib (BAY 43-9006) is a potent inhibitor of various tyrosine kinases such as vascular endothelial growth factor receptor (VEGFR), KIT, or PDGFR which is currently approved for advanced renal carcinoma and under evaluation for other malignancies.[37]

Sorafenib was found to inhibit imatinib-resistant proliferative activities of FIP1L1-PDGFRA T674I mutated tyrosine kinase in Ba/F3 cells and was found to induce apoptosis of the EOL-1 cell line.[38] When given in a patient with chronic eosinophilic leukaemia and FIP1L1-PDGFRα T674I mutation in blast crisis, a clinical response was promptly achieved. Unfortunately, this was short-lived as a sorafenib-resistant FIP1L1-PDGFRalpha D842V mutant developed rapidly that responded to sorafenib (Nexavar).[39] Another mutation S601P conferring dual imatinib/orafenib resistance was subsequently identified in a FIP1L1-PDGFRA positive HES patient.[40]

PKC412

PKC412 is a staurosporine derivative currently under evaluation as an antitumour therapy for various malignancies, which was initially demonstrated to inhibit protein kinase C and several tyrosine kinases including PDGFR, FLT3 or VEGF.[41]

When tested in FIP1L1-PDGFRA positive or FIP1L1-PDGFRA T674I Ba/F3 cells lines PKC412 demonstrated its suppressing effects whereas in a murine model of bone marrow transplantation of FIP1L1-PDGFRA T674I induced myeloproliferative disease, it prolonged survival and reduced white cell counts and spleen weight significantly when compared with placebo or imatinib-treated animals.[42,43]

Dasatinib

Dasatinib (BMS-354825) is another pluripotent kinase inhibitor for Bcr-Abl, KIT, or PDGFRB which was found to also be active against imatinib-resistant Bcr-Abl isoforms and to inhibit T-cell activation and proliferation.[44,45] Dasatinib was found to be effective in patients with chronic myeloid leukaemia or with Bcr-Abl-positive acute lymphoblastic leukaemia after imatinib therapy failure and the fact that it targets kinases involved in HES pathogenesis might also qualify it to also be assessed in this condition.[46]

ANTI-INTERLEUKIN-5 THERAPIES: MEPOLIZUMAB, RESLIZUMAB

In the lymphoproliferative HES subset the pathogenic mechanism is represented by a deregulation of T-cell homeostasis, with generation of abnormal Th2 clones upregulated to produce increased levels of IL-5, IL-4 and other cytokines/chemokines involved in eosinophil proliferation and activation and in B-cell differentiation with increased IgE production.[47] The most frequently described clone was a CD4+(Th2) lymphocyte population lacking CD3 membrane expression (CD3-CD4+).[48] The fact that IL-5 is produced by eosinophils might also raise the issue of differentiating HES subsets and the clue for achieving this would be demonstration of a Th2-driven 'cytokine profile': IL-5, IL-4, IL-13, IL-3, and GM-CSF in lymphoproliferative HES forms.[6]

Interleukin-5 has also evolved as another therapeutic target in HES. As mentioned above, it is not only produced by Th2 lymphocytes but also by eosinophils or basophils/mast cells. It upregulates eosinophil counts and activities via an IL-5 receptor, which is a heterodimer with an IL-5 specific binding chain α (IL-5Rα) expressed only on eosinophils and basophils and a non-ligand chain β, which is common to GM-CSF and IL-3 receptors as well.[49] IL-5Rα selectivity for eosinophils explains IL-5 complex involvement in proliferation, differentiation, activation and survival of these cells and qualified it to be tackled with various specific therapies in different allergic diseases including asthma.[50] Hypereosinophilic syndromes were also included in investigational plans for two anti-IL-5 therapies: SCH55700 and mepolizumab.

SCH55700 is a humanised murine monoclonal anti-IL-5 neutralising antibody of the IgG4/κ subtype.[51] A single 1 mg/kg dose of SCH55700 was tested in four patients with HES refractory/intolerant to conventional therapies and was found to produce a normalisation of the peripheral eosinophil count and to improve organ symptoms and signs. Therapeutic response was not found to be predicted by serum interleukin-5 (IL-5) levels or by presence of the FIP1L1/PDGFRA mutation. An eosinophil-lowering effect was found to last up to 12 weeks but a rebound of eosinophil count and symptoms were reported when levels of the compound decreased. SCH55700 retreatment given on a monthly basis reduced eosinophilia and symptoms, but the amplitude of therapeutic effect was lower when compared with original treatment.[52]

Rebound eosinophilia, which is reported to occur after SCH55700 treatment, was found to be due to an upregulating factor hypothesised to be IL-5 itself. High levels of IL-5 were found in sera retrieved one month after SCH55700 treatment and *in vitro* SCH55700 post-treatment sera retrieved from patients with HES and eosinophilic gastroenteritis with peripheral eosinophilia were found to prolong survival of normal eosinophils, unlike pretreatment sera. This effect was reversed by the murine monoclonal anti-IL-5 antibody TRFK5.[53]

A single dose of SCH55700 was also tested clinically in a pilot study in a small sample of asthma subjects with severe persistent asthma despite oral or high doses of inhaled corticosteroids, and was found to reduce, in a dose-dependent manner, blood eosinophilia and to improve lung function, without demonstrating a significant effect on clinical outcome measures of disease activity.[54]

SB-240563 (mepolizumab) is the other humanised mouse monoclonal anti-IL-5 antibody of the IgG1/κ subtype which was evaluated for HES, asthma or other eosinophilic disorders: the first report of therapeutic efficacy of mepolizumab in a HES patient showed that three subsequent weekly doses of 750 mg mepolizumab significantly reduced peripheral eosinophilia, IL-5 levels and organ-related symptoms; however rebound eosinophilia was reported to occur rapidly, within days after the last dosage, and was also reported in other subsequent studies performed in other eosinophilic conditions.[55]

In a subsequent case series including three patients with FIP1L1-PDGFRA negative corticosteroid-resistant HES and related severe dermatitis, mepolizumab 750 mg of mepolizumab doses were given at a two weekly interval for variable durations ranging from five to eight months: after the initial two mepolizumab infusions which were associated with significant clinical and haematological improvement, disease rebound was reported in two of the three patients.[56]

In an open-label study mepolizumab was given intravenously every four weeks for 12 weeks in four FIP1L1-PDGFRA negative HES patients, most of them having multiple organ involvement: blood eosinophilia was found to decrease rapidly and significantly in three of these four patients, with the effect lasting at least eight weeks after the last dosage. Health-related quality of life was found to be improved as well as lung function and no rebound eosinophilia was reported.[57]

Mepolizumab therapy given as a 750 mg infusion every four weeks for a 36-week period was subsequently tested in a randomised, double-blind, placebo-controlled trial in 85 FIP1L1-PDGFRA negative HES patients receiving prednisone monotherapy, 20 to 60 mg per day. The primary endpoint of efficacy (reduction of the prednisone dose to ≤10 mg/day for ≥8 consecutive weeks) was reached in 84% of the patients treated with monoclonal antibody compared with 43% of patients in the placebo group (HR, 2.90; $p<0.001$). A peripheral blood eosinophilia count of <600/μl for ≥8 consecutive weeks was achieved in 95% of patients receiving mepolizumab, as compared with 45% of patients receiving placebo (HR 3.53; $p<0.001$). Serious adverse events occurred in seven patients receiving mepolizumab and in five patients receiving placebo.[58]

When the therapeutic effects of three-monthly infusions of mepolizumab on peripheral blood eosinophil counts were assessed in 25 patients with various eosinophilic diseases; 23 were found to respond to anti-IL-5 therapy with a significant reduction in peripheral eosinophil counts. Haematological responsiveness was not related to the levels of baseline plasma IL-5 or the presence of FIP1L1-PDGFRA fusion gene. The effect persisted three months after final infusion in 76% of subjects. However, mepolizumab therapy was associated with an increase in IL-5 serum levels due to generation of an IL-5-mepolizumab precipitating complex. [59]
Mepolizumab was planned to be launched on the market with the commercial name of Bosatria but the application was withdrawn based on inconclusive risk-benefit data.[60]

ALENTUZUMAB: ANTI-CD 52 MONOCLONAL ANTIBODY

CD52 is a surface protein expressed by human eosinophils. An *in vitro* study evaluating expression and functional activity of CD52 on human eosinophils and neutrophils of healthy donors and hypereosinophilia patients showed that only eosinophils expressed this protein. Preincubation of eosinophils with mouse anti-CD52 monoclonal antibody alone, and preincubation of eosinophils with mouse anti-CD52 and cross-linking by goat antimouse antibody resulted in a significant inhibition of reactive oxygen species production after stimulation with C5a. A similar effect was found after incubation with humanised anti-CD52 monoclonal antibody and cross-linked by goat antihuman antibody and was reported to occur on eosinophils retrieved from patients with hypereosinophilia.[61]
Alemtuzumab (CAMPATH) is a humanised monoclonal anti-CD52 which was evaluated initially in three cases with HES refractory to conventional therapy and to imatinib, one of them exhibiting CD3-CD4+ abnormal phenotype: alemtuzumab resulted in sustained haematological and clinical responses.[62,63] More recently, alemtuzumab was given in weekly cycles at a dose of 30 mg or 10 mg three times per week either intravenously or subcutaneously in a pilot study involving nine patients with FIP1L1-PDGFRA-negative HES who had previously received conventional therapies and various tyrosine kinase inhibitors. Complete haematological remission was detected in eight patients within the first four weeks of therapy; alemtuzumab withdrawal in five patients resulted in a disease flare after a median period of 3.5 weeks.[64]
In another study 11 patients with advanced HES/CEL received alemtuzumab therapy, first in escalating doses (5, 10, 30 mg intravenously on days 1-3) followed by the titrated tolerated dose three times a week for a total of 12 doses. In patients with a complete haematological response (i.e. normalisation of the peripheral blood eosinophil count) once-weekly maintenance therapy was given. Complete haematological response was achieved in ten patients (91%) after a median of two weeks therapy and lasted three months (median duration). Bone marrow abnormal eosinophilia disappeared in four of seven evaluable patients. Subsequently seven of the ten patients relapsed, five after therapy cessation. Alemtuzumab retreatment resulted in a second complete haematological remission in two patients. Cytomegalovirus reactivation was reported in two patients and orbital lymphoma successfully treated in one patient.[65]

CONCLUSIONS

Hypereosinophilic syndromes include various phenotypes defined based on the immunogenetic abnormality, which results in abnormal bone marrow and organ eosinophil proliferation. Currently three main disease subsets are considered: HES/CEL or FIP1L1-PDGFRA positive subset, lymphoproliferative HES and 'idiopathic' HES.
In the HES/CEL subset, IM is currently recommended to be the first-line therapy given its demonstrated inhibitory activities on FIP1L1-PDGFRA fusion protein. Fortunately in HES, reports of IM resistance are not common and this still preserves its therapeutic effectiveness. However, when this occurs, this may pose a significant therapeutic challenge. There might be several mutations rending the abnormal tyrosine kinase more abnormal, this time from a therapeutic point of view but T674I is currently reported to occur most frequently in HES.
Therefore newer tyrosine kinase inhibitors have to face this 'genetic provocation' and to demonstrate a better efficacy and safety as compared with IM.
The long-term efficacy of the anti-IL-5 monoclonal antibodies in the lymphoproliferative form of HES is unclear and questionable due for example in the case of mepolizumab to the rapid development of rebound eosinophilia. Studies discussed in this review focused on this aspect too, but further data are needed in order to gain a better picture on this phenomenon. One (with luck the only) major reason for such behaviour might be represented by the immunogenicity of such compounds: the existing anti-IL-5 monoclonal antibodies are *humanised* rat-derived compounds and this structural particular might at least in theory increase the risk of immunogenicity. The fact that rebound eosinophilia was reported to occur quite rapidly after initial anti-IL-5 antibodies and if immungenicity only is to be considered, this might reflect a certain 'immune aggressivity' of such compounds in the specific HES setting which indeed undermines their efficacy. Given these facts,

feasible options would be to test existing investigational anti-IL-5 therapies combined to corticosteroids or other immunosuppressive therapies, to discover newer fully human monoclonal antibodies or other therapies targeting Th2-related IL-5 pathway.

Alemtuzumab is also a promising anti-eosinophil therapy. It has the disadvantage of treating the end-effect which, however, can be inversely seen as a major advantage as the end pathogenic effect in HES is the same irrespective of the genetic and/or immune pathogenic defects. However, more clinical data on this compound are needed including findings on long-term safety.

Overall many of the novel therapies for HES discussed above seem to be promising if further evaluated and appropriately tested and, given that newer therapeutic approaches are desirable especially in subsets such as idiopathic HES, supportive data are essential.

Recent reclassification of HES subsets led to a certain 'individualisation' of its therapies according to disease subset: the major benefit is represented by a more appropriate therapeutic targeting which consequently results in a better disease outcome. However, this therapeutic targeting seems to be unevenly distributed among the subsets and this yields an inadequate therapeutic coverage of some disease subsets. In this respect there is a need to discover other therapies for HES subsets with unmet therapeutic.

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