ADIS DRUG EVALUATION

Drugs 2006; 66 (1): 111-131
0012-6667/06/0001-0111/$44.95/0

Anagrelide

A Review of its Use in the Management of Essential Thrombocythaemia

Antona J. Wagstaff and *Gillian M. Keating*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

T. Barbui, Division of Haematology, Ospedali Riuniti di Bergamo, Bergamo, Italy; ***G. Birgegård***, Department of Internal Medicine, University Hospital, Uppsala, Sweden; ***E. Cacciola***, Department of Biological Sciences, Hematology Section, Ferrarotto Hospital, Catania, Italy; ***R.R. Cacciola***, Department of Biological Sciences, Hematology Section, Ferrarotto Hospital, Catania, Italy; ***G. Finazzi***, Division of Haematology, Ospedali Riuniti di Bergamo, Bergamo, Italy; ***M. Mazzucconi***, Department of Biocellular Technology and Hematology, La Sapienza University, Rome, Italy; ***J.J. Michiels***, Department of Haematology, Goodheart Institute Rotterdam, Rotterdam, The Netherlands; ***F.C. Molinas***, Sección Hematologia Investigación, Instituto de Investigaciones Médicas Alfredo Lanari, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina; ***F. Passamonti***, Division of Hematology, IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; ***A. Tefferi***, Division of Hematology, Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA; ***A. Tomer***, Blood Bank and Transfusion Medicine, Faculty of Health Sciences, Soroka University Medical Center, Beer-Sheva, Israel.

Data Selection

Sources: Medical literature published in any language since 1980 on anagrelide, identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were'anagrelide' or 'BL-4162A'. The EMBASE and AdisBase search term was 'anagrelide'. Searches were last updated 19 December 2005.

Selection: Studies in patients with essential thrombocythaemia who received anagrelide. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Anagrelide, essential thrombocythaemia, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary 112
1. Introduction 114
2. Pharmacodynamic Properties 115
   2.1 Effects on Bone Marrow/Platelets 115
   2.2 Cardiovascular Effects 116
3. Pharmacokinetic Properties 117
   3.1 General Properties 117
   3.2 Special Patient Groups 118
4. Therapeutic Efficacy 118
   4.1 Platelet Counts 120
      4.1.1 Prospective Noncomparative Trials 120
      4.1.2 Retrospective Studies 120
      4.1.3 Versus Hydroxycarbamide 121

4.2 Thrombohaemorrhagic Symptoms/Events 121
4.2.1 Versus Hydroxycarbamide 121
4.2.2 Noncomparative Trials 121
4.3 Disease Transformation 122
4.4 Pharmacoeconomic Considerations 123
5. Tolerability 123
5.1 General Profile 123
5.2 Cardiovascular Effects 124
6. Dosage and Administration 125
7. Place of Anagrelide in the Management of Essential Thrombocythaemia 125

Summary

Abstract

Anagrelide (Agrylin®, Xagrid®) is an oral imidazoquinazoline agent which is indicated in Europe for the reduction of elevated platelet counts in at-risk patients with essential thrombocythaemia who are intolerant of or refractory to their current therapy, and in the US for the reduction of elevated platelet counts and the amelioration of thrombohaemorrhagic events in patients with thrombocythaemia associated with myeloproliferative disorders.

Anagrelide is well established as an effective platelet-lowering agent in most patients with essential thrombocythaemia, including both treatment-naive patients and those refractory to other cytoreductive therapy. Results of the only randomised trial to date (the Primary Thrombocythaemia 1 [PT1] study) indicated that the composite primary endpoint (arterial or venous thrombosis, serious haemorrhage or death from vascular causes) occurred more often in recipients of anagrelide plus aspirin than in those receiving hydroxycarbamide (hydroxyurea) plus aspirin. This trial also indicated that the incidence of the secondary endpoints transient ischaemic attack and gastrointestinal bleeding favoured hydroxycarbamide plus aspirin, while the incidence of venous thrombosis favoured anagrelide plus aspirin. There were no differences between the groups in the incidence of secondary endpoints myocardial infarction, stroke, unstable angina, pulmonary embolism, hepatic-vein thrombosis, other serious haemorrhage or related deaths. The design of the PT1 study has been queried with respect to the heterogeneous nature of the study population (possible inclusion of patients with early myelofibrotic disease) and the concomitant use of aspirin (interaction with anagrelide causing increased bleeding events). Further data are therefore required before the role of anagrelide in essential thrombocythaemia can be finalised. In the meantime, when considering treatment options for patients with this disorder, anagrelide's positive effects on platelet function, lack of mutagenicity and lack of association with leukaemia or angiogenesis must be balanced against its comparative expense and positive inotropic effects. Thus, the role of anagrelide in the management of high-risk patients with essential thrombocythaemia will ultimately depend on individual patient assessment and future clarification of the potential leukaemogenicity of hydroxycarbamide.

Pharmacological Properties

Anagrelide and its active metabolite 3-hydroxy anagrelide specifically, reversibly and dose-dependently block the maturation of late-stage megakaryocytes, thus reducing platelet counts in patients with essential thrombocythaemia. The drug appears to normalise platelet coagulant and endothelial function, does not stimulate myelofibrotic progression and, unlike hydroxycarbamide, is not associated with angiogenesis or damage to DNA. The inhibitory effect of anagrelide, and particularly of the 40-fold more potent 3-hydroxy anagrelide, on phosphodiesterase III results in positive inotropic effects (vasodilation, and increased heart rate and contractility) and potential for pharmacodynamic interactions with other phosphodiesterase inhibitors.

The pharmacokinetics of anagrelide are linear in the 0.5–2mg dose range. After oral administration, anagrelide is rapidly absorbed and the drug is metabolised, mainly during first pass, to two main metabolites, the active 3-hydroxy anagrelide and the inactive 5,6-dichloro-3,4-dihydroquinazol-2-ylamine. Peak plasma concentrations of anagrelide and the active metabolite are reached in about 2 hours. Systemic exposure to 3-hydroxy anagrelide is about twice that of the parent compound in patients with essential thrombocythaemia. The terminal half-lives of anagrelide and the active metabolite are 1.7 and 3.9 hours in this patient group. Since metabolism occurs primarily via cytochrome P450 1A2, interactions with drugs such as fluvoxamine are possible. There is no evidence of an interaction with hydroxycarbamide, digoxin or warfarin. Individual titration of dosages allows the effects of age or hepatic or renal impairment to be taken into consideration.

Therapeutic Efficacy

Early noncomparative trials have clearly indicated that anagrelide lowers platelet counts in most (complete plus partial response in 82–98%; complete response in 38–88%) patients with essential thrombocythaemia. Complete response rates of approximately 50% were seen in patients who were unresponsive to previous hydroxycarbamide treatment in two small trials. Clinically significant reductions usually occurred well within the first month of treatment. Anagrelide and hydroxycarbamide (each with concomitant aspirin) reduced platelet counts to a similar extent after 9 months' treatment in the randomised nonblind PT1 trial in high-risk patients with essential thrombocythaemia, but hydroxycarbamide appeared to act more quickly.

Previous experience of arterial or venous thrombosis or haemorrhage was relatively high at baseline in the PT1 trial. The overall composite primary endpoint of serious thrombohaemorrhagic events favoured hydroxycarbamide. Secondary endpoints indicated that while anagrelide plus aspirin was superior to hydroxycarbamide plus aspirin as measured by the lower incidence of deep-vein thrombosis, hydroxycarbamide plus aspirin was superior with respect to the incidence of transient ischaemic attacks and serious gastrointestinal haemorrhage. There were no differences between the groups in the individual incidences of myocardial infarction, stroke, unstable angina pectoris, pulmonary embolism, hepatic-vein thrombosis, other serious haemorrhages or death from thrombosis or haemorrhage. The concomitant administration of aspirin in the PT1 trial is thought to have resulted in a synergistic action resulting in increased bleeding events.

Essential thrombocythaemia was less likely to progress to myelofibrosis in hydroxycarbamide recipients than in anagrelide recipients in the PT1 trial; howev-

er, the baseline risk for myelofibrosis was not taken into account in the diagnostic methodology, with subsequent potential for imbalance of prefibrotic conditions. The incidence of transformation to acute myeloid leukaemia/myelodysplasia or polycythaemia vera and deaths from transformation were similar in the two groups, although follow-up was possibly inadequate for reliable estimation.

Tolerability

The most common adverse events associated with oral anagrelide are headache, palpitations, diarrhoea, asthenia, oedema, nausea, abdominal pain and dizziness. The incidence and severity of many adverse events decreases with extended treatment in some but not all patients. The incidence of serious adverse events is higher in older patients. Cardiovascular effects such as congestive heart failure or arrhythmia are uncommon. Palpitations, headache, noncardiac oedema, diarrhoea and abdominal pain were more common in recipients of anagrelide plus aspirin than in those receiving hydroxycarbamide plus aspirin in the PT1 trial of high-risk patients with essential thrombocythaemia. Dermatological events (mainly leg ulcers) and diabetes mellitus occurred more often with hydroxycarbamide and white-cell counts were persistently lower in this group. There were no differences between the groups in the incidence of other gastrointestinal symptoms, anaemia, cardiac failure, arrhythmia or minor haemorrhage.

1. Introduction

Essential thrombocythaemia is a myeloproliferative disorder which is associated with a sustained increase in the number of platelets in peripheral blood. Recent investigations have indicated that an acquired mutation on the Janus kinase 2 gene (Jak2V617F) is present in many patients with myeloproliferative disorders, including essential thrombocythaemia.[1] Although 50–70% of patients with essential thrombocythaemia have no symptoms at presentation,[2] characteristic symptoms can develop over the course of the disease. These include microvascular complications caused by spontaneous activation and aggregation of hypersensitive thrombocythaemic platelets (peripheral paraesthesia of the extremities, headache, dizziness, visual disturbances, erythromelalgia, transient ischaemic attacks), thromboembolic complications (pulmonary embolism, splenic infarction, arterial or venous thrombosis, angina pectoris, myocardial infarction) and haemorrhagic complications (oral, intracerebral, gastrointestinal or cutaneous bleeding).[3,4]

Essential thrombocythaemia, which current evidence indicates occurs in about 2.5 per 100 000 person-years,[5] is commonly diagnosed according to criteria initially devised by the Polycythaemia Vera Study Group (PVSG).[6] The amended criteria comprise a platelet count $>600 \times 10^9$/L for ≥2 months and no evidence of reactive thrombocytosis, polycythaemia vera, iron deficiency, chronic myeloid leukaemia, myelofibrosis or myelodysplastic syndrome.[7] Since diagnosis is largely a matter of exclusion, the resulting patient cohort with essential thrombocythaemia is likely to be heterogeneous. When bone marrow histopathology is included as a diagnostic feature, as in the WHO criteria for essential thrombocythaemia, patients with prefibrotic or early fibrotic chronic idiopathic myelofibrosis are excluded.[8,9] Patients diagnosed using the PVSG criteria are thus much more likely to progress to overt myelofibrosis.[8] The discovery of the Jak2V617F mutation in patients with myeloproliferative disorders will also have repercussions on the future diagnosis, classification and treatment of essential thrombocythaemia.[1]

Life expectancy does not appear to be affected in patients with essential thrombocythaemia,[10,11] especially in those diagnosed using bone marrow histopathology.[8] Older patients and those having experienced a previous thrombotic event are considered to be high-risk patients.[11,12] The incidences of

major thrombotic and haemorrhagic events in patients with essential thrombocythaemia, the cause of much of the morbidity and mortality associated with the disease, have been estimated at 7–17% and 8–14%, respectively, in retrospective cohort studies using a wide variety of inclusion criteria, clinical settings and event definitions.[13] Major thrombotic complications have been estimated to occur at a rate of 3–4% per patient-year in low-risk patients and 11% per patient-year in high-risk patients.[13] The cause of clonal evolution of essential thrombocythaemia into idiopathic myeloid metaplasia, myelodysplastic syndrome or acute myeloid leukaemia is not yet clear. While some advocate the presence of a small but real risk of delayed transformation occurring as a result of natural disease progression,[5] others suggest that transformation may be caused by cytoreductive therapy or a mixture of both intrinsic and extrinsic factors.[12]

Anagrelide (Agrylin®, Xagrid®)[1] is an oral imidazoquinazoline agent with platelet-lowering activity in humans.[3] This review focuses on the efficacy and tolerability of anagrelide in the treatment of adults with essential thrombocythaemia.

2. Pharmacodynamic Properties

2.1 Effects on Bone Marrow/Platelets

The mechanism of action of anagrelide has not yet been fully characterised. The lack of animal models of the thrombocytopenic effects of anagrelide (which are more evident in humans than in laboratory animals) has limited study of the pharmacodynamic effects of the drug.[14]

Essential thrombocythaemia is associated with hyperproliferation of megakaryocytes, with increased cell size and ploidy (higher proportions of 32N or higher ploidy cells versus healthy controls), and a mean platelet turnover rate about six times higher than that in healthy controls.[15] Anagrelide and its active metabolite 3-hydroxy anagrelide (section 3.1) specifically prevent megakaryocyte differentiation *in vitro*.[16] 3-Hydroxy anagrelide, like the parent compound, has a marked effect on megakaryocyte growth and is similar in potency and specificity to anagrelide in this respect.[16] The development of megakaryocytes was inhibited by 50% at concentrations of 26 and 44 nmol/L by anagrelide and 3-hydroxy anagrelide, respectively.[16] It is likely that 3-hydroxy anagrelide contributes substantially to the clinical platelet-lowering effects of the formulation, considering the higher systemic exposure to the metabolite than to the parent compound (section 3.1).[17]

Anagrelide dose-dependently and reversibly prevents the maturation of megakaryocytes in nonmitotic late stages of development (the size, surface irregularity, optical density and ploidy of the megakaryocytes are reduced),[15,18-20] which results in increased numbers of precursor cells (promegakaryoblasts and megakaryoblasts).[20] The number of megakaryocytes may also be decreased by anagrelide.[15]

Anagrelide does not affect haematopoietic stem cells and does not damage DNA.[21,22] Oral treatment with either anagrelide or hydroxycarbamide (hydroxyurea) resulted in increased incidence of promegakaryoblasts and microforms in 20 patients with initial to early-stage chronic idiopathic myelofibrosis and thrombocythaemia in a bone marrow immunohistochemical and morphometric study.[22] However, while no such changes were seen with anagrelide, hydroxycarbamide was associated with significant abnormalities of megakaryocytic differentiation indicative of dysplastic changes and therefore of leukaemogenic potential.[22]

The platelet turnover rate is reduced close to normal rates but platelet survival is unaffected in patients with essential thrombocythaemia receiving anagrelide.[15,23] Thus, oral anagrelide caused reversible reductions in platelet counts in healthy volunteers[3] and platelet counts were normalised in patients with essential thrombocythaemia.[24,25] This thrombocytopenic effect, however, does not occur in all patients (see section 4).

In contrast to hydroxycarbamide and interferon-α, anagrelide does not appear to be associated with

1 The use of trade names is for product identification purposes only and does not imply endorsement.

bone marrow angiogenesis in patients with essential thrombocythaemia.[20,26] Levels of platelet count-corrected vascular endothelial growth factor (VEGF) and platelet factor 4 (PF4), markers of angiogenesis, were increased at baseline versus those in healthy controls and were normalised with anagrelide therapy; however, levels were increased further in patients receiving hydroxycarbamide or interferon-α (n = 13).[26] Similarly, bone marrow vessel-related CD34+ progenitor cell levels, also used to mark angiogenesis, were not increased by anagrelide (n = 15).[20]

Many abnormal aspects of platelet function associated with essential thrombocythaemia are improved with anagrelide treatment. Platelet count-corrected thromboxane B2 values tended toward normalisation in 17 patients with essential thrombocythaemia during anagrelide-induced remission.[27] Similarly, platelet coagulant activity and endothelial function (PF4, prothrombin fragment 1+2, plasmin/α2-antiplasmin complex, plasminogen activator inhibitor-1, tissue factor pathway inhibitor) were normalised in 17 patients with essential thrombocythaemia who responded to anagrelide.[28] In this and other studies, normalisation of endothelial function was associated with disappearance of erythromelalgic symptoms (see also section 4.2).[27,28]

Both anagrelide and its active metabolite inhibit platelet cyclic adenosine monophosphate phosphodiesterase (PDE)III and phospholipase A_2,[15,16] an effect that is independent of the effects on megakaryocyte differentiation.[16] 3-Hydroxy anagrelide, is nearly 40 times more potent than anagrelide in inhibiting PDEIII, an effect with possible cardiovascular consequences (see section 2.2).[17] While significant inhibition of platelet aggregation appears only to occur at plasma anagrelide concentrations higher than those required for the thrombocytopenic effect, 3-hydroxy anagrelide has some anti-aggregatory activity at therapeutic concentrations as suggested by its greater anti-PDEIII potency.[17] The effects of anagrelide on the abnormal platelet aggregation seen in some patients with essential thrombocythaemia are as yet unresolved. Spontaneous aggregation in unmodified whole blood and defective platelet aggregation (i.e. no response to epinephrine and/or low response to adenosine diphosphate or collagen) were not improved by anagrelide in several small studies in patients with essential thrombocythaemia.[3,15,24] However, spontaneous platelet aggregation (measured in platelet-rich plasma using an aggregometer) occurring in six of 17 patients with essential thrombocythaemia before treatment with anagrelide did not occur in five of these six after anagrelide-induced normalisation of platelet counts.[29]

While baseline plasma platelet-derived growth factor (PDGF) levels were higher and intraplatelet PDGF levels were lower in 15 patients with essential thrombocythaemia than in healthy controls, these returned to near normal levels in most patients receiving anagrelide for ≥2 months.[30] Anagrelide had little effect on the increased plasma levels of other growth factors involved in myelofibrosis (transforming growth factor-β and basic fibroblast growth factor) in these patients.[30] In line with these results, there was no evidence of a stimulating effect of anagrelide, after a median duration of about 2 years, on the progression of myelofibrosis as assessed using bone marrow biopsies in two small studies (one prospective: n = 17;[31] one retrospective: n = 15[20]).

While there are no reports of increased bleeding associated with anagrelide monotherapy,[21] there are indications that the addition of aspirin to anagrelide treatment can synergistically increase the incidence of bleeding in patients with essential thrombocythaemia (section 4.2.1),[32-35] possibly as a result of the known effects of aspirin being aggravated by the vasodilating effect of anagrelide (section 2.2). In a 6-month study in patients with myeloproliferative disorders (n = 97), bleeding events occurred in nine patients receiving anagrelide plus concomitant low-dose aspirin versus two receiving anagrelide alone (figure 1).[36]

2.2 Cardiovascular Effects

Anagrelide-associated decreased peripheral vascular resistance and blood pressure and increased heart rate and positive inotropic effects (increased

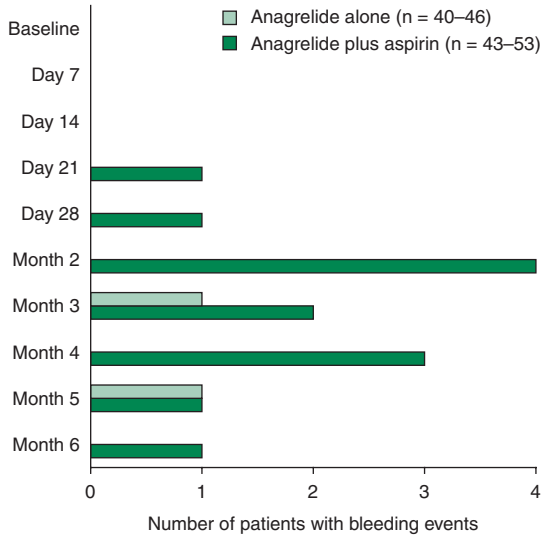

Fig. 1. Bleeding events in patients receiving oral anagrelide with and without concomitant aspirin. Patients with myeloproliferative disorders (n = 97) who were at high risk of complications if untreated or who were refractory to or intolerant of previous treatment with hydroxycarbamide or interferon-α received anagrelide 1–2 mg/day for 6 months, with or without concomitant low-dose aspirin (numbers receiving aspirin varied during treatment), in a noncomparative prospective trial.[36] Some patients had more than one bleeding event.

ventricular contractility) noted in preclinical studies have since been confirmed in humans, although blood pressure appears to return to baseline levels during maintenance therapy.[3,19] Vasodilation, as shown by increases in microvascular area in anagrelide recipients[20] as a consequence of the PDEIII-inhibiting effects of the drug, can cause headache, fluid retention, dizziness and postural hypotension, and occasionally serious cardiovascular disease such as congestive heart failure (section 5).[19,37,38]

The main contributor to the cardiovascular effects of anagrelide is likely to be the active metabolite, 3-hydroxy anagrelide.[17] Because of the inhibitory effect of anagrelide and its metabolite on PDEIII, concomitant administration of drugs such as milrinone, enoximone, amrinone, olprinone or cilostazol may result in exacerbation of their effects.[34]

3. Pharmacokinetic Properties

Most of the pharmacokinetic data on oral anagrelide in this section were obtained from the Citizen Petition submitted to the US FDA by the manufacturers[17] or the manufacturers' prescribing information.[34,35]

3.1 General Properties

An overview of the pharmacokinetic properties of anagrelide is given in table I. The kinetics are linear in the dose range 0.5–2mg.[35] Peak plasma anagrelide concentrations (C_{max}) are reached in 2 hours in patients with essential thrombocythaemia (table I), and anagrelide does not accumulate in plasma with repeated administration.[35] Absorption of anagrelide is extensive, as evidenced by recovery in the urine of >70% of an oral 1mg radiolabeled dose to healthy volunteers.[39] However, the absolute oral bioavailability is thought to be <50%.[17]

The terminal half-life of the parent compound is 1.7 hours.[17] Anagrelide is rapidly metabolised to two main metabolites, the active 3-hydroxy anagrelide (BCH24426) and the inactive 5,6-dichloro-3,4-dihydroquinazol-2-ylamine (RL603) [figure 2].[16,17] 3-Hydroxy anagrelide is largely formed via first-pass metabolism by the cytochrome P450 (CYP)1A2 enzyme.[17] Exposure to 3-hydroxy anagrelide is higher than to the parent compound (table I).[17] In patients with essential thrombocythaemia, systemic exposure was higher and the elimination half-life was longer than in healthy volunteers (table I).

Table I. Overview of anagrelide pharmacokinetics. Mean variables for anagrelide and its active metabolite 3-hydroxy anagrelide were normalised to a 1mg dose and 70kg bodyweight after oral administration to adult healthy volunteers and patients with essential thrombocythaemia (ET)[17]

	Healthy volunteers (n = 38)		Patients with ET (n = 18)	
	anagrelide	3-hydroxy anagrelide	anagrelide	3-hydroxy anagrelide
AUC_{∞} (ng • h/mL)	11.1	18.0	19.5	44.1
C_{max} (ng/mL)	5.0	5.5	6.2	8.7
t_{max} (h)	1.3	1.3	2.0	2.3
$t_{½}$ (h)	1.5	2.5	1.7	3.9

AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; **C_{max}** = maximum plasma concentration; **t_{max}** = time to C_{max}; **$t_{½}$** = elimination half-life.

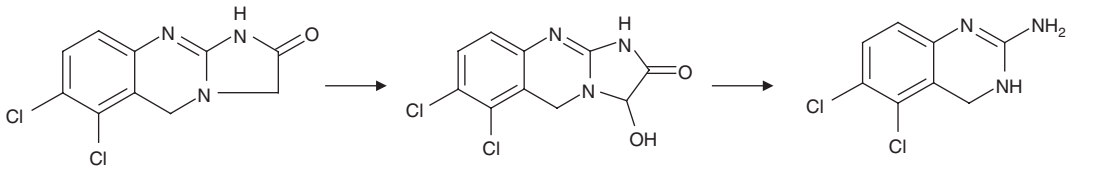

Fig. 2. Summary of the metabolic pathway of anagrelide in healthy volunteers.[16]

The effect of food on the bioavailability of anagrelide is complex. While the C_{max} of the parent compound is decreased by about 14% and the area under the plasma concentration-time curve (AUC) is increased by about 20% in the presence of food, C_{max} of 3-hydroxy anagrelide is decreased by about 30% and AUC is unaffected by food.[17]

Less than 1% of unchanged drug is recovered in the urine.[34] The elimination of anagrelide could be slowed by interaction with drugs such as fluvoxamine, or by grapefruit juice (which inhibit CYP1A2).[34] Similarly, the elimination of drugs like theophylline could be affected by concomitant ingestion of anagrelide.[34] There is no evidence of a pharmacokinetic interaction between anagrelide and hydroxycarbamide, digoxin or warfarin.[34]

3.2 Special Patient Groups

The time to C_{max} and the elimination half-lives of anagrelide, 3-hydroxy anagrelide and 5,6-dichloro-3,4-dihydroquinazol-2-ylamine were similar for paediatric (aged 7–14 years) and adult (aged 16–86 years) patients with thrombocythaemia associated with a myeloproliferative disorder.[35] However, dose- and bodyweight-normalised exposure (C_{max} and AUC) for anagrelide in paediatric patients was about half that in older adult patients, implying more efficient clearance in the younger age group.[35]

While severe renal impairment does not appear to affect the pharmacokinetics of anagrelide, total exposure (AUC) to anagrelide after a single 1mg dose was 8-fold higher in subjects with moderate hepatic impairment than in healthy subjects.[35,40]

4. Therapeutic Efficacy

While response rates involving control of the platelet count alone have been useful for phase II studies of treatment of essential thrombocythaemia, investigations at later stages should assess changes in the natural history of the disease and alleviation of disease-related complications, with associated improvements in quality of life. The main focus of the early noncomparative trials of oral anagrelide in patients with essential thrombocythaemia was on reduction of platelet counts (section 4.1); however, the focus of the one available randomised trial (the Primary Thrombocythaemia 1 [PT1] trial)[33] was on the effects of anagrelide or hydroxycarbamide on the occurrence of vascular events (section 4.2).

In the nonblind, multicentre PT1 trial, high-risk adult patients with essential thrombocythaemia were randomised to treatment with oral anagrelide at an initial dosage of 0.5mg twice daily (n = 405) or hydroxycarbamide 0.5–1 g/day (n = 404) for a median of 39 (range 12–72) months.[33] Dosages of both drugs were adjusted to maintain platelet counts at $<400 \times 10^9$/L. All patients received concomitant aspirin 75–100 mg/day (n = 792) or, if aspirin was contraindicated, dipyridamole (n = 13) or clopidogrel (n = 4) [dosages not reported]. Diagnosis was made using the criteria of the PVSG.[6] The patients were at high risk of thrombotic or haemorrhagic vascular events (criteria included age >60 years, platelet count $\geq 1000 \times 10^9$/L, or a history of ischaemia, thrombosis, embolism or haemorrhage caused by essential thrombocythaemia, or hypertension or diabetes mellitus requiring drug therapy). Patients were excluded from the study if they had the t(9;22) translocation or *BCR-ABL* fusion gene, myelodysplasia, myelofibrosis or causes of thrombocytosis,

Table II. Efficacy of oral anagrelide in patients (pts) with essential thrombocythaemia (ET). Summary of noncomparative, prospective clinical studies in pts (aged 14–83 [median 33–59] years) with myeloproliferative disorders including or restricted to ET

Study	Diagnosis and no. of evaluable pts [% with symptoms]	Previously[a] untreated pts (%)	PC ($\times 10^9$/L) [mean unless otherwise indicated]	Pts receiving concomitant therapy	Anagrelide dosage (mg/d)[b] initial	maintenance [mean]	Duration of therapy	Response defined as reduction in PC[c] to:	Response rate (%)
Basara et al.[41][d]	ET 20, PV 14, CML 4 [NR]	NR	[1220]	NR	20	NR	NR	<600 or 50%	95
Birgegård et al.[14]	ET 42, PV 17, MF 1 [NR]	55	>600 (SP) or >1000 (AP)	ASP: 47%	1	[2.2]	2y	CR: <400 (SP) or <600 (AP); PR: ≤50%	CR: 67; PR: 6; ETCR: 76; ETPR: 6
Kornblihtt et al.[42]	ET 54 [67]	44	520–2206 [995]	NR	1–3	0.5–5.5 [1.5]	0.8–14.3 [med 6] y	CR: <400; PR: 400–600	CR: 78; PR: 18
Mazzucconi et al.[43]	ET 39 [31]	62	>650 (SP) or ≥900 (AP) [1197]	ASP: 0	1	1–3 [2]	0.5–12.5 [med 6] y	CR: <450; PR: 450–600	CR: 38; PR: 44[e]
Mazur et al.[44]	ET 40 [NR]	0	[1136]	NR	NR	1–3.5 [2]	8–54 [med 23] mo	CR: ≤450	CR: 55; PR: 43
Mills et al.[45]	ET 16 [81]	0	>600 [728]	ASP: 31%; WAR: 38%; HDC: 13%	1–2	1–3 [1.9]	3mo	CR: <400; PR: <600	CR 44; PR 44
Petrides et al.[46]	ET 48 [85]	33	>600 (SP) or >900 (AP) [1193]	ASP: 54%	2	1–12 [3.1]	1–84 [med 12.5] mo	CR: ≤600 and 50%; PR: 50–80%	CR: 88; PR: 6
Steurer et al.[36]	ET 79, PV 16, MF 2 [57[f]]	29[g]	335–1912 [med 743]	ASP: 55%; IFN or HDC: 20%	1	0.5–4.5 [med 2]	6mo	CR: <450; VGPR: <600; PR: <50% but >600	CR: 52; VGPR: 26; PR: 2

a In most trials, patients were transferred from previous therapy because of lack of efficacy or occurrence of unacceptable adverse events.[36,43-46]

b Given in divided doses.

c Reductions are given as goal PC x 10^9/L or as a percentage of baseline PC. Where specified, the reduction was to be maintained for ≥4wk.[14,36,41,43,46]

d Abstract.

e Of nine pts with high baseline PC (≥1500 x 10^9/L), six achieved CR and two PR.

f Of these, 29 patients (30%) had thromboembolic complications (6% major and 24% minor) during the 6mo before the study.

g Newly diagnosed pts had to be high-risk for inclusion.

AP = asymptomatic pts; **ASP** = aspirin; **CML** = chronic myeloid leukaemia; **CR** = complete response; **ETCR/ETPR** = CR or PR in pts with ET; **HDC** = hydroxycarbamide; **IFN** = interferon-α; **med** = median; **MF** = myelofibrosis; **NR** = not reported; **PC** = platelet count; **PR** = partial response; **PV** = polycythaemia vera; **SP** = symptomatic pts; **VGPR** = very good partial response; **WAR** = warfarin.

breathlessness, cardiac pain, myocardial infarction in the previous 3 months, severe congestive heart failure, severe ventricular arrhythmia or leg ulceration, or were pregnant/lactating. About 30% had received previous hydroxycarbamide treatment and 18% had received no prior treatment.[33]

The composite primary efficacy endpoint in this study comprised death from thrombosis or haemorrhage, or occurrence of arterial thrombosis, venous thrombosis or serious haemorrhage.[33] Secondary endpoints included occurrence of the first arterial or venous thrombotic event, serious haemorrhage or death, incidence of transformation to myelofibrosis, acute myeloid leukaemia, myelodysplasia or polycythaemia vera, and platelet count. All endpoints were independently reviewed/validated by clinicians blinded to treatment assignment.

Of the reviewed noncomparative trials, eight were prospectively designed (table II) and two were multicentre;[14,36] patients were followed for up to 12.5 years. Three of these trials enrolled patients with other myeloproliferative disorders (i.e. polycythaemia vera, chronic myeloid leukaemia, myelofibrosis); however, in these trials, most patients (53–81%; n = 20–79) had essential thrombocythaemia.[14,36,41] The other trials limited enrolment to patients with essential thrombocythaemia (n = 16–48).[42-46] Diagnosis was mostly made using the criteria of the PVSG,[6] although one trial[14] used the criteria of Kutti and Wadenvik which include bone marrow histology.[47] In selected trials, entry was restricted to patients who had been previously treated with myelosuppressive agents,[45] or patients with essential thrombocythaemia refractory to previous hydroxycarbamide.[44] The proportion of previously untreated patients ranged from 29% to 62% in the other trials, where reported.[14,36,42,43,46] Two trials reported inclusion of a washout period before initiation of anagrelide therapy.[14,43] Anagrelide was given initially at 1–2 mg/day (most studies indicated divided doses) and maintenance doses were adjusted thereafter to achieve target platelet counts (table II). The primary endpoint (reduced platelet counts) was defined in two trials.[36,43]

One retrospective study has been included because of its size.[2] Patients in this study had thrombocythaemia associated with myeloproliferative disorders, were aged 5–98 years and received an initial anagrelide dosage of 2 mg/day. The 934 patients with essential thrombocythaemia in this trial were followed for >7 years; 18% of these patients received concomitant hydroxycarbamide and many received aspirin during the study; 76% had received previous medication; 31% were receiving anagrelide because of poor platelet control with previous therapy.[2]

Although patient numbers were small (n = 35), a second retrospective study was included because 27 of the 33 responding patients had received anagrelide for an extended period (7–16 [median 11] years).[48] Younger patients (aged 17–48 years) were chosen for this trial to circumvent confounding problems associated with age and comorbid conditions. Before treatment, 27 patients had symptomatic disease (history of thrombosis 20%, haemorrhage 26%, vasomotor manifestations 51%), and 24 patients had received hydroxycarbamide or busulfan therapy. Oral anagrelide was administered at an initial dosage of 1–10 mg/day.

4.1 Platelet Counts

4.1.1 Prospective Noncomparative Trials

Anagrelide reduces platelet counts in patients with essential thrombocythaemia. Although response criteria in all the trials required reduced platelet counts, the exact definitions of complete and partial response varied among the trials, and results specific to patients with essential thrombocythaemia were not given in all trials (see table II). Nonetheless, the overall (complete plus partial) response rates tended to be high for the reviewed trials, ranging from 82% to 98% in patients with essential thrombocythaemia.[14,42-46] Complete responses were seen in 38–88% of patients with essential thrombocythaemia.[14,42-46] In two small trials of patients with essential thrombocythaemia refractory to previous treatment (mainly hydroxycarbamide), complete response rates were 44% and 55%, and overall response rates were 88% and 98%.[44,45]

The time to reach a response, where reported, varied from 6 days to 12 months (median, given in four trials, ranged from 2 weeks to 4 months[14,42-44]);[14,41,43-45] this broad range was possibly dependent to some extent on variations in the rate of dosage increase during the early stages of therapy. Some response is usually reached within the first 2 weeks.[42]

4.1.2 Retrospective Studies

The large retrospective study showed that a clinically significant reduction (complete plus partial response) in platelet counts occurred in 79% of patients with essential thrombocythaemia on receipt of oral anagrelide therapy (83% of previously untreated patients).[2] A complete response (the primary endpoint; 67% of patients) was defined as reduction in platelet count of ≥50% from baseline or to

≤600 × 10^9/L for ≥4 weeks. A partial response (12%) was defined as reductions of 20–50% from baseline. Mean platelet counts were reduced from 1090 × 10^9/L to <600 × 10^9/L at 2 months and to 470–480 × 10^9/L from the end of the first year.[2]

The initial overall response to anagrelide in the long-term retrospective study in younger patients[48] was 94%, comprising complete remission (a sustained platelet count of <450 × 10^9/L) in 26 patients, partial remission (450–600 × 10^9/L) in seven patients and no response in two patients.[48] Of the 29 evaluable patients who received anagrelide (at a maintenance dosage of 1–5 [median 2.5] mg/day) for the duration of the study, 19 (66%) were in complete remission and ten (34%; six of these had initially experienced complete remission) were in partial remission at final follow-up.

4.1.3 Versus Hydroxycarbamide

Anagrelide and hydroxycarbamide, given with concomitant aspirin to high-risk patients, reduced platelet counts to a similar extent at 9 months of treatment and thereafter (from baseline medians of 930 and 947 × 10^9/L, respectively, to 370 × 10^9/L for both; estimated from a graph).[33] However, at the earlier timepoints of 3 and 6 months, platelet counts were lower in the group receiving hydroxycarbamide plus aspirin (370 and 330 × 10^9/L) than in those receiving anagrelide plus aspirin (450 and 370 × 10^9/L) [estimated from a graph; $p < 0.001$ for both 3 and 6 months]. The numbers of patients achieving platelet counts <400 × 10^9/L at various timepoints was not reported.

4.2 Thrombohaemorrhagic Symptoms/Events

4.2.1 Versus Hydroxycarbamide

Arterial or venous thrombosis, serious haemorrhage or death from vascular causes (composite primary endpoint) occurred more often in recipients of anagrelide plus aspirin than in those receiving hydroxycarbamide plus aspirin (55 vs 36 patients; odds ratio 1.57; 95% CI 1.04, 2.37; $p < 0.05$; figure 3) in the PT1 trial.[33] The estimated risk (after a median of 39 months' follow-up) of this endpoint occurring at 5 years of treatment was 16% with anagrelide versus 11% with hydroxycarbamide.

The groups were matched for baseline thrombohaemorrhagic experience and time from diagnosis to enrolment; 6% had previous venous thromboembolism, 18% had previous arterial thrombosis and 6% had previous haemorrhage. The overall secondary endpoint of venous thrombosis was more common in hydroxycarbamide plus aspirin recipients than in those receiving anagrelide plus aspirin (14 [4%] vs 3 [1%]; $p < 0.01$), while arterial thrombosis (17 [4%] vs 37 [9%]) and serious haemorrhage (8 [2%] vs 22 [5%]) each occurred significantly more often in recipients of anagrelide plus aspirin (both $p < 0.01$). However, the study was not powered to differentiate to this level, and these results may have been subject to selection bias or chance.

Among the individual parameters making up the secondary endpoints (figure 3), a significant difference in favour of anagrelide plus aspirin was seen for deep-vein thrombosis (1 vs 9 patients; $p < 0.01$). Significant differences in favour of hydroxycarbamide plus aspirin were seen for transient ischaemic attack (1 vs 14 patients; $p < 0.001$) and gastrointestinal bleeding (3 vs 13 patients; $p = 0.01$). There were no significant differences between the groups for other arterial thromboses (myocardial infarction, stroke or unstable angina), venous thromboembolisms (pulmonary embolism or hepatic-vein thrombosis) or serious haemorrhages (nasal, intracranial or other), and there were no significant differences between the groups in the incidence of death from thrombosis or haemorrhage.

4.2.2 Noncomparative Trials

Five of the prospective trials included an indication of the number of patients (31–85% of the total cohorts; table II) with thrombohaemorrhagic symptoms often associated with thrombocythaemia (e.g. microvascular circulation disturbances, transient ischaemic attacks, headache/dizziness, cutaneous symptoms, etc.) at baseline or a history of thrombohaemorrhagic events (e.g. stroke, myocardial or pulmonary infarction, bleeding requiring transfusion).[36,42,43,45,46] Symptoms improved and/or there

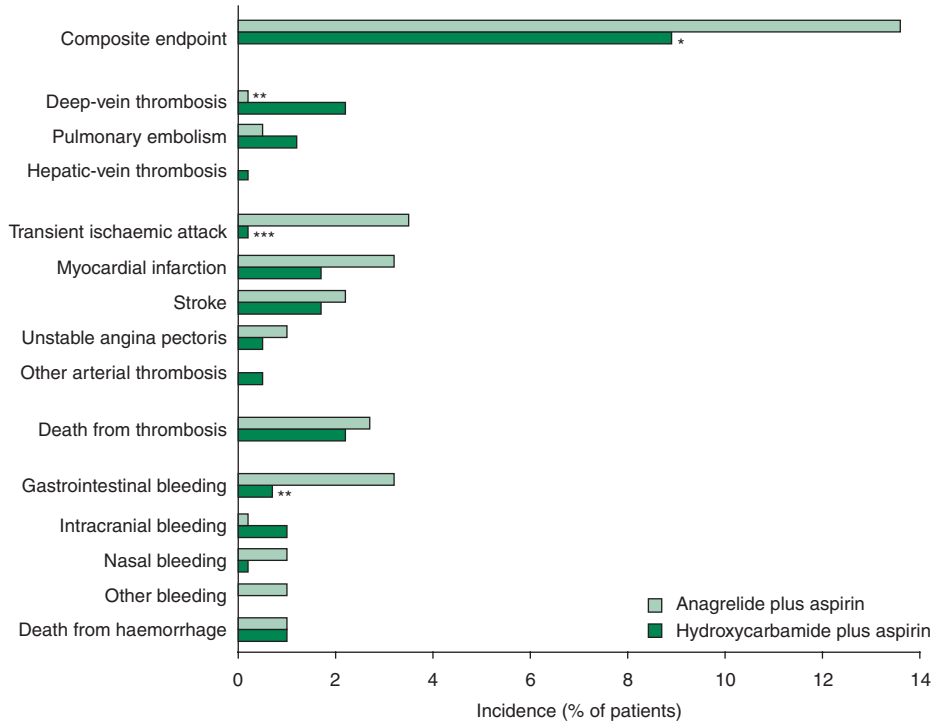

Fig. 3. Comparative efficacy of oral anagrelide plus aspirin in high-risk patients with essential thrombocythaemia. Incidence of venous or arterial thrombosis, serious haemorrhage or death from thrombosis or haemorrhage (the composite endpoint) and individual secondary thrombohaemorrhagic endpoints in patients at high risk of vascular events randomised to treatment with anagrelide (initial dosage 0.5mg twice daily; n = 405) or hydroxycarbamide (initial dosage 0.5–1 g/day; n = 404) for a median of 39 months in a nonblind, multicentre study.[33] Dosages were adjusted to achieve a platelet count of $<400 \times 10^9$/L. All patients received concomitant aspirin, dipyridamole or clopidogrel. * $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ vs comparator.

was no recurrence of previous complications in 50–100% of patients during anagrelide therapy of 3 months to 6 years' duration in the three studies providing this information.[29,36,45] In one study, symptoms disappeared in all patients with a platelet count response during long-term therapy (median 73 months; number of responding patients not reported).[43] Others found that symptoms reappeared in some patients (8–13%) despite continued platelet count reduction.[42,44]

Thrombotic events (none fatal) occurred in seven patients (20%) and major haemorrhagic events (one fatal; three gastrointestinal) occurred in seven patients (20%) during anagrelide treatment in the long term, retrospective study in young patients.[48] In all the affected patients, the platelet count was $>400 \times 10^9$/L at the time of the event.

4.3 Disease Transformation

The rate of development of myelofibrosis was significantly lower in recipients of hydroxycarbamide plus aspirin versus anagrelide plus aspirin in the PT1 trial (figure 4).[33] Comparative baseline histology-based risk factors for transformation to myelofibrosis were not, however, presented. Myelofibrotic transformation was defined as at least grade 3 reticulin fibrosis in a bone marrow biopsy (plus an increase by ≥1 grade from baseline), plus at least two of: increased spleen size by ≥3cm; decreased haemoglobin by ≥20 g/L; immature myeloid or erythroid cells in blood smear; tear-drop poikilocytes in blood smear; or night sweats, bone pain or weight loss of >10% in 6 months.

There were no significant differences between the groups in the rate of transformation to acute

myeloid leukaemia/myelodysplasia or polycythaemia vera or death from transformation (figure 4).[33] However, 39 months' follow-up is possibly inadequate for estimating the total risk in this respect.

Of the 2251 anagrelide recipients with essential thrombocythaemia evaluable for disease transformation analysis in a large retrospective study, 47 patients (2%) developed acute leukaemia/myelodysplastic syndrome, mostly within the first year of treatment.[2] All 47 patients had received previous cytotoxic drug treatment.

4.4 Pharmacoeconomic Considerations

Two pharmacoeconomic direct-cost analyses using Markov models based on noncomparative phase II clinical trial data indicate that, despite its relatively high purchase price, anagrelide could be cost effective in some scenarios.[49,50]

In one study, the cost effectiveness of anagrelide treatment for essential thrombocythaemia improved over 1 year from the first 3 months of treatment

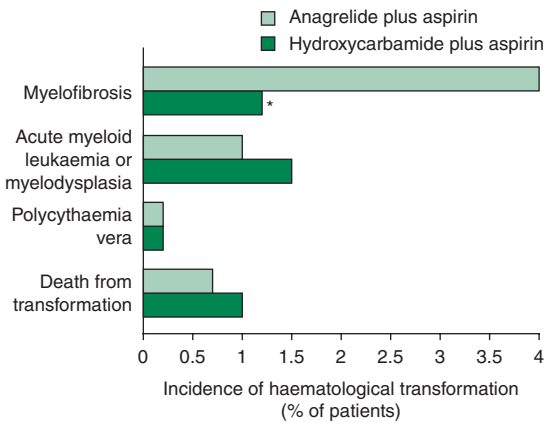

Fig. 4. Comparative haematological transformation with anagrelide plus aspirin in patients with essential thrombocythaemia at high risk of vascular events. Patients were randomised to treatment with oral anagrelide (initial dosage 0.5mg twice daily; n = 405) or hydroxycarbamide (initial dosage 0.5–1 g/day; n = 404) for a median of 39 months in a nonblind, multicentre study.[33] Dosages were adjusted to achieve a platelet count of $<400 \times 10^9$/L. All patients received concomitant aspirin, dipyridamole or clopidogrel. Transformation occurred in the anagrelide and hydroxycarbamide groups at a median of 45 and 34 months after diagnosis for myelofibrosis and 83 and 36 months after diagnosis for acute myeloid leukaemia. * $p < 0.05$.

($US2462 per major complication [gastrointestinal bleed, transient ischaemic attack, stroke, preinfarction angina, myocardial infarction] prevented; year of costing not reported) to 10–12 months ($US1505).[49]

The other analysis, conducted from a societal perspective, found that lifelong treatment with anagrelide for a 40-year-old man with essential thrombocythaemia was associated with a marginal cost effectiveness versus hydroxycarbamide of $US71 737 per year of life gained.[50] If hydroxycarbamide was associated with an assumed risk of disease transformation to leukaemia of 0.1 and the threshold willingness for society to pay was $US75 000, anagrelide was optimal in 66% of 1000 trials; however, hydroxycarbamide was optimal in all trials when the willingness to pay was reduced to $US50 000. Further, if the hydroxycarbamide-associated risk of transformation to leukaemia was reduced to 0.05, the incremental cost effectiveness of anagrelide increased to $US156 969 per additional life-year gained. Interferon-α was associated with higher costs and lower efficacy than anagrelide. The study used an annual discount rate of 3% and was published in 2002 (year of costing not reported).

5. Tolerability

Information for this section was drawn mainly from the manufacturers' prescribing information[34] and selected clinical studies[2,14,33,48] (see section 4 for design details).

5.1 General Profile

The tolerability profile of anagrelide at a mean dosage of about 2 mg/day for up to 4 years in 942 patients from three noncomparative studies and 3660 patients in a further noncomparative study (34 took anagrelide for up to 5 years) has been outlined by the manufacturers in the prescribing information.[34,35] The most common adverse events in the 942-patient cohort were headache (44%), palpitations (26%), diarrhoea (26%), asthenia (23%), oedema (21%), nausea (17%), abdominal pain (16%) and dizziness (15%).[35] Other common events occurring in anagrelide recipients at an incidence of 5–15%

included other pain, dyspnoea, flatulence, vomiting, fever, peripheral oedema, rash, anorexia, tachycardia, pharyngitis, malaise, cough, paraesthesia, pruritus and dyspepsia; most adverse events were mild in intensity.[35] Serious adverse events that occurred rarely during anagrelide therapy included congestive heart failure, myocardial infarction, cardiomyopathy, cardiomegaly, complete heart block, atrial fibrillation, cerebrovascular accident, pericarditis, pericardial effusion, pleural effusion, pulmonary infiltrates, pulmonary fibrosis, pulmonary hypertension, pancreatitis, gastric/duodenal ulceration and seizure.[35] The incidence/severity of adverse events in anagrelide recipients is dose-dependent.[14] The incidence of serious adverse events was twice as high in patients aged ≥60 years than in younger patients in a retrospective study of 2251 patients with essential thrombocythaemia.[2]

Anaemia occurs commonly in anagrelide recipients,[34] possibly as a result of the vasodilating effects of anagrelide.[14] Mean haemoglobin levels dropped significantly and dose-dependently in the first few weeks of anagrelide treatment (from a baseline of 13.2 g/dL to a nadir of 12.7 g/dL in week 8), and remained lower than baseline during a prospective, 2-year trial in 60 patients with myeloproliferative disorders (70% with histologically confirmed essential thrombocythaemia).[14] In contrast, anaemia developed later, after approximately 1–10 years of anagrelide treatment, in four of 39 patients (aged 22–52 years) with histologically confirmed essential thrombocythaemia in another prospective trial.[43] Thrombocytopenia and pancytopenia are listed by the manufacturers as uncommon (<1% of patients).[34]

The incidence of adverse events falls with extended treatment in some patients. For example, in a retrospective study of younger patients (aged 17–48 years) who received anagrelide for up to 16 (median 11) years, the incidence of headache dropped from 34% in the first 3 months to 6% long term.[48] Similarly, initial and long-term incidences of tachycardia were 23% and 9%, of oedema were 14% and 6% and of diarrhoea were 9% and 0%. However, a prospective, noncomparative, 2-year study (n = 60),[14] with tolerability as one of the primary objectives, found that although adverse events abated to some extent during the initial months of therapy, the intensity of adverse events remained unchanged in many patients with prolonged treatment. In fact, withdrawal from anagrelide treatment because of adverse events was high in this study: patients discontinued treatment because of insufficient efficacy at a tolerable dosage (n = 13), adverse events despite complete response (n = 10) or other reasons unrelated to tolerability (n = 7). Fifty percent of patients remained on anagrelide treatment after 2 years. The most common and severe adverse events in this study were headache, palpitations and diarrhoea.

The number of patients withdrawing from treatment because of adverse events in the randomised PT1 trial in 809 high-risk patients with essential thrombocythaemia was higher in those receiving anagrelide plus aspirin than in those receiving hydroxycarbamide plus aspirin (22% vs 11%; $p < 0.001$).[33] Headache (13% vs 2%; $p < 0.001$), diarrhoea (4% vs 1%; $p = 0.01$), abdominal pain (2% vs <1%; $p < 0.01$) and noncardiac oedema (6% vs 1%; $p < 0.001$) were more common with anagrelide than with hydroxycarbamide. However, dermatological events such as leg or mouth ulcers (11% vs 7%; $p = 0.05$) and diabetes (2% vs 1%; $p = 0.05$) occurred more often with hydroxycarbamide than with anagrelide. From 3 months after initiating treatment, median white-cell counts were significantly and persistently lower in hydroxycarbamide recipients than in anagrelide recipients. There were no significant differences between the groups in the incidence of minor haemorrhage, nausea/vomiting, peptic ulcer/oesophagitis/gastritis, anaemia or thrombocytopenia/neutropenia.

5.2 Cardiovascular Effects

While palpitations, tachycardia and fluid retention were common in patients receiving anagrelide in studies monitored by the manufacturers (occurring in 1–10% of patients), congestive heart failure, hypertension, arrhythmia, atrial fibrillation, supraventricular/ventricular tachycardia, syncope, oedema and chest pain were uncommon (0.1–1%),

and angina pectoris, myocardial infarction, cardiomegaly, pericardial effusion, vasodilatation, migraine and postural hypotension were rare (0.01–0.1%) [see also section 2.2].[34]

Palpitations (including irregular pulse) occurred in 16% and 2% of anagrelide and hydroxycarbamide recipients in the PT1 trial ($p < 0.001$).[33] There were no significant differences between the groups in the incidence of cardiac failure or arrhythmia.

6. Dosage and Administration

Anagrelide is available in Europe, the US and numerous other countries worldwide. In Europe, anagrelide has orphan drug status and is indicated for the reduction of elevated platelet counts in at-risk patients with essential thrombocythaemia who are intolerant of or refractory to their current therapy. Patients at risk are defined as those >60 years of age, those with a platelet count $>1000 \times 10^9$/L, or those with a history of thrombohaemorrhagic events.[34] In the US, anagrelide is indicated for the treatment of patients with thrombocythaemia associated with myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohaemorrhagic events.[35]

The anagrelide package inserts currently recommend a starting oral dosage for adults of 0.5mg twice daily (Europe) or 0.5mg four times daily or 1mg twice daily (US); this dosage should be maintained for ≥1 week and thereafter titrated individually to achieve a platelet count $<600 \times 10^9$/L and ideally $150–400 \times 10^9$/L.[34,35] Although experience in children is limited, starting dosages have ranged from 0.5 mg/day (recommended in the US[35]) to 0.5mg four times daily. Dosages should be increased by no more than 0.5 mg/day in a single week, and should not exceed 10 mg/day. The recommended maximum single dose is 2.5mg.

Patients with cardiovascular disease (see also section 2.2) or hepatic dysfunction (section 3.2) should be monitored closely during anagrelide therapy. Dosage reduction is recommended for patients with moderate hepatic impairment in the US and the drug is contraindicated in patients with moderate or severe hepatic impairment in Europe. There is no contraindication or warning in the US for the use of anagrelide in patients with renal impairment but the drug is contraindicated in both moderate and severe impairment (creatinine clearance <50 mL/min) in Europe.[34,35,40]

In addition to the potential pharmacokinetic interactions with drugs inhibiting CYP1A2 outlined earlier (section 3.1), anagrelide may also have synergistic anti-aggregatory effects when given with aspirin (section 2.1). For additional dosage and administration information, the local manufacturer's prescribing information should be consulted.

7. Place of Anagrelide in the Management of Essential Thrombocythaemia

The primary aim of treatment for essential thrombocythaemia is to reduce the incidence of the main causes of morbidity and mortality: thrombohaemorrhagic events and disease transformation to myelofibrosis or acute leukaemia.[13] Because of the adverse effects associated with cytoreductive agents, particularly the leukaemogenic propensity of some, the treatment of low-risk patients remains controversial, with many advocating administration of cytotoxic therapy on the basis of their risk for developing vascular events (i.e. no treatment for low-risk patients).[12]

The available treatment guidelines outline the at-risk patient groups for whom platelet-lowering therapy is recommended in Italy (table III).[13] Consensus could not be reached on whether patients aged 40–60 years who have platelet counts $<1000 \times 10^9$/

Table III. Recommendations from Italian haematology societies[13] on specific patient groups requiring platelet-lowering therapy for essential thrombocythaemia

All patients aged >60 years
All patients aged <60 years with a history of major thrombotic or haemorrhagic events
All patients with platelet counts $>1500 \times 10^9$/L
Patients aged 40–60 years with platelet counts $>1000 \times 10^9$/L and a cardiovascular risk factor or familial thrombophilia
Patients aged <40 years with prothrombotic comorbidity (homocysteinuria, familial dominant hypercholesterolaemia)
Patients with severe microcirculatory symptoms

Table IV. Italian guidelines for choice of platelet-lowering agent in patients with essential thrombocythaemia who are eligible for such treatment[13]

Patient group	First-line therapy	Alternative therapy[a]	Other factors
Patients aged <40y, no child-bearing potential	IFNα or ANA	HDC	HDC not recommended in very young patients
Patients aged 40–60y, no child-bearing potential, with a history of a major thrombotic event	HDC		
Patients aged 40–60y, no child-bearing potential, without a history of a major thrombotic event	IFNα or ANA[b]		Use of ANA should be monitored by entry into trials or a register
Women with child-bearing potential	IFNα	ANA (second-line) → HDC (third-line)	Patients should stop taking ANA or HDC if pregnancy is suspected
During pregnancy[c]	IFNα		
Patients starting therapy aged 60–70y	HDC	BUS or PIP	Patients already successfully receiving IFNα or ANA should continue
Patients aged >70y	HDC, BUS or PIP		Patients already successfully receiving IFNα or ANA should continue

a Second-line or subsequent treatment options if adverse effects affect quality of life or high doses increase toxicity.

b Since publication of the PT1 trial,[33] some members of the Italian group are now considering HDC plus aspirin as first-line therapy in this patient group.[12,32]

c Treatment is recommended if there is a history of major thrombosis or haemorrhage, platelet counts $>1000 \times 10^9$/L, familial thrombophilia or cardiovascular risk factors.

ANA = anagrelide; **BUS** = busulfan; **HDC** = hydroxycarbamide; **IFNα** = interferon-α; **PIP** = pipobroman; **PT1** = Primary Thrombocythaemia 1.

L and no history of major thrombohaemorrhagic events but who have a cardiovascular risk factor or familial thrombophilia should be treated. The associated guidelines for choice of platelet-lowering agent in specific treatment-eligible patient groups, outlined in table IV, were prepared by an Italian expert panel and advisory committee[13] at a time when reliable comparative scientific evidence was scarce. Guidelines for the treatment of essential thrombocythaemia remain in a state of flux as data from ongoing long-term trials become available and diagnostic and classification changes are assessed.

Treatment of essential thrombocythaemia traditionally involves administration of platelet-lowering agents and/or anti-platelet agents (e.g. aspirin, clopidogrel). Anti-platelet agents have been recommended for patients with microcirculatory symptoms if there are no contraindications and for patients with recent major arterial vascular events or coronary artery disease if no previous significant bleeding has occurred.[13]

The most commonly used platelet-lowering agents other than anagrelide are hydroxycarbamide, a nonspecific myelosuppressive agent that reduces all myelogenous lineages via inhibition of DNA synthesis, and recombinant interferon-α, a cytokine that inhibits the growth of multipotent haematopoietic progenitor cells and megakaryocyte-forming units.[13] Hydroxycarbamide reduced the incidence of thrombotic episodes versus no treatment in patients with essential thrombocythaemia,[51] but is associated with dose-limiting haematopoietic impairment, oral or leg ulcers and other skin lesions.[52] Adverse oral or skin effects, including leg ulcers, occurred at a rate of 26% in 133 patients receiving hydroxycarbamide for >2 years, generally appearing ≥5 years after starting treatment and often necessitating withdrawal from treatment.[53] There remains some uncertainty about whether hydroxycarbamide is leukaemogenic. There were no cases of leukaemic or neoplastic transformation in one study of previously untreated patients with essential thrombocythaemia (aged <50 years) receiving hydroxycarbamide alone for a median of 8 (range 5–14) years.[54] However, other studies report therapy-related leukaemic transformation associated with

hydroxycarbamide in previously untreated patients,[55,56] and long-term follow-up (6 years) of patients with essential thrombocythaemia in a randomised study of hydroxycarbamide versus no therapy found that the absent or very low risk of leukaemic progression in untreated patients (no cases in this study) was increased slightly with hydroxycarbamide alone (4%).[57] Further, recent histological evidence supports the potential of this drug for leukaemogenic conversion (section 2.1). The rate of transformation is increased when hydroxycarbamide is given with other agents.[52] Until this issue is clarified, it has been suggested that hydroxycarbamide should not be administered to very young patients (table IV).[13,58]

While interferon-α is not leukaemogenic, it does have to be given parenterally and is associated with severe adverse effects (e.g. fatigue, depression, influenza-like symptoms, elevated liver enzymes, anorexia, alopecia, neuropsychiatric symptoms) often necessitating withdrawal.[52] Interferon-α is recommended by some for cytoreductive treatment of high-risk women planning pregnancy (table IV).

Pipobroman (which has a structural resemblance to alkylating agents) is clinically active in patients with essential thrombocythaemia.[59] However, this and the alkylating agent busulfan have been associated with development of secondary acute leukaemia, myelodysplastic syndromes or solid tumours,[57,59,60] especially in patients receiving concomitant or subsequent hydroxycarbamide.[57] Marketing of pipobroman has been discontinued in the US,[61] and busulfan is now rarely used to treat essential thrombocythaemia.[14]

Anagrelide is clearly an effective platelet-lowering agent in both untreated patients and those refractory to previous hydroxycarbamide (section 4.1). In addition, this drug tends to normalise platelet function defects associated with essential thrombocythaemia and has anti-angiogenic properties (section 2.1).

The comparative position of anagrelide in the management of essential thrombocythaemia has not been widely studied to date. Interpretation of the results of the recently published PT1 trial of anagrelide plus aspirin versus hydroxycarbamide plus aspirin in high-risk patients is partly hindered by the use of PVSG diagnostic criteria in the study and by its early termination.[33] As outlined earlier (section 1), the use of bone marrow biopsy in the diagnostic process, which was not included in the design of this trial, allows specific subtypes of patients, with differing prognostic outcomes, to be distinguished. Recent studies have found that, of cohorts of patients initially diagnosed according to PVSG criteria, only about one-third had true essential thrombocythaemia according to WHO (histology-based) criteria.[8,9] The remaining patients had thrombocythaemia associated with prefibrotic or early fibrotic chronic idiopathic myelofibrosis. This patient distribution may well have been repeated in the PT1 trial of anagrelide versus hydroxycarbamide.[33] Further, a recent publication indicates that essential thrombocythaemia patients with the Jak2V617F mutation are more likely to benefit from hydroxycarbamide than from anagrelide treatment, a hypothesis that deserves further investigation.[62] While anagrelide does not affect progression of early fibrotic stages to classical myelofibrosis (section 2.1), hydroxycarbamide may slow fibrotic progression, as demonstrated in the PT1 trial (section 4.3). It thus seems reasonable to assume that the reported risk of myelofibrotic transformation in the anagrelide arm was not related to treatment, but to the heterogeneity of disease in the included patients.

The safety of concomitant platelet-lowering/antiplatelet therapy remains under discussion. The results of the PT1 trial[33] suggest that an interaction between anagrelide and aspirin may have increased the risk of haemorrhage (see also section 2.1), an outcome that requires further research and potential modification of current recommendations. While bleeding has not traditionally been a problem in patients receiving anagrelide monotherapy (section 2.1), gastrointestinal haemorrhage is known to be associated with aspirin use in patients with polycythaemia vera or essential thrombocythaemia.[63] Aspirin may also have exacerbated bleeding in patients with acquired von Willebrand syndrome,

common in patients with elevated platelet numbers.[21,63]

The event rates were low in the PT1 trial despite the size of the study cohort and follow-up of over 3 years. Both anagrelide and hydroxycarbamide are effective agents in this respect; both decreased the number of disease-related events compared with historical records for untreated controls.[51] Anagrelide plus aspirin was associated with a decreased rate of deep-vein thrombosis and an increased rate of transient ischaemic attacks versus hydroxycarbamide plus aspirin in high-risk patients with essential thrombocythaemia in the PT1 trial (section 4.2). Since low-dose aspirin is highly effective in the prevention of platelet-mediated microvascular disturbances such as erythromelalgia and transient ischaemic attacks,[4] the excess incidence of transient ischaemic attacks in anagrelide recipients in this trial may have been associated with the known cardiac effects of anagrelide (section 2.2).

Anagrelide is not mutagenic (section 2.1) and there is no evidence to date to suggest that it is leukaemogenic. Further data from well designed trials (using specific diagnostic criteria) on this and thrombohaemorrhagic outcomes would be helpful. A phase III, randomised, single-blind, multicentre comparison of the efficacy and tolerability of anagrelide versus hydroxycarbamide in high-risk previously untreated patients with essential thrombocythaemia (the AOP 03-007 ANAHYDRET [ANAgrelide HYDRoxyurea in patients with Essential Thrombocythaemia] study) is currently under way.[64]

Anagrelide is associated with headache, palpitations and diarrhoea, as well as the development of cardiovascular effects (section 5), necessitating ongoing monitoring of patients and possible dosage adjustments. It has been suggested that the risk of thrombosis is increased in patients who only partially respond to anagrelide (i.e. platelet counts $>400 \times 10^9$/L);[48] there is therefore a need to clarify the optimal target platelet count for patients with essential thrombocythaemia in randomised trials. Since adverse events associated with anagrelide are dose-related, the administration of high enough doses to achieve this target may not be possible in some, particularly elderly, patients.

Because the treatment of essential thrombocythaemia will be long term, and patients with this disorder are expected to achieve near normal lifetimes, long-term efficacy and tolerability of potential medications are important factors for consideration. Experience with anagrelide in children is limited to case reports that indicate potential for efficacy with only minor adverse effects.[65-69] There is some evidence of long-term (11 years) efficacy (section 4.1.2), and reduction in the incidence of adverse effects with time (section 5), in young adults receiving anagrelide.

While two related pharmacoeconomic analyses have indicated that anagrelide is cost effective in some scenarios (section 4.4), these analyses were based on noncomparative clinical trials and were sensitive to the leukaemogenic potential of hydroxycarbamide. Further pharmacoeconomic analyses based on well designed comparative trials are awaited with interest.

In conclusion, anagrelide is well established as an effective platelet-lowering agent in most patients with essential thrombocythaemia, including both treatment-naive patients and those refractory to other cytoreductive therapy. Results of the only randomised trial to date (the PT1 study) indicated that the composite primary endpoint (arterial or venous thrombosis, serious haemorrhage or death from vascular causes) occurred more often in recipients of anagrelide plus aspirin than in those receiving hydroxycarbamide plus aspirin. This trial also indicated that the incidence of the secondary endpoints transient ischaemic attack and gastrointestinal bleeding favoured hydroxycarbamide plus aspirin, while the incidence of venous thrombosis favoured anagrelide plus aspirin. There were no differences between the groups in the incidence of other arterial or thrombotic embolisms or haemorrhagic secondary endpoints. However, the design of the PT1 study has been queried with respect to the heterogeneous nature of the study population (possible inclusion of patients with early myelofibrotic disease) and the concomitant use of aspirin (interaction with anagre-

lide causing increased bleeding events). Further data are therefore required before the role of anagrelide in essential thrombocythaemia can be finalised. In the meantime, when considering treatment options for patients with this disorder, anagrelide's positive effects on platelet function, lack of mutagenicity and lack of association with leukaemia or angiogenesis must be balanced against its comparative expense and positive inotropic effects. Thus, the role of anagrelide in the management of high-risk patients with essential thrombocythaemia will ultimately depend on individual patient assessment and future clarification of the potential leukaemogenicity of hydroxycarbamide.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

References

1. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloprolerative disorders. Lancet 2005 Mar 19; 365 (9464): 1054-61
2. Fruchtman SM, Petitt RM, Gilbert HS, et al. Anagrelide: analysis of long-term efficacy, safety and leukemogenic potential in myeloproliferative disorders. Leuk Res 2005; 29 (5): 481-91
3. Spencer CM, Brogden RN. Anagrelide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of thrombocythaemia. Drugs 1994 May; 47 (6): 809-22
4. Michiels JJ, Berneman ZN, Schroyens W, et al. Pathophysiology and treatment of platelet-mediated microvascular disturbances, major thrombosis and bleeding complications in essential thrombocythaemia and polycythaemia vera. Platelets 2004 Mar; 15 (2): 67-84
5. Tefferi A, Silverstein MN. Treatment of polycythaemia vera and essential thrombocythaemia. Baillieres Clin Haematol 1998 Dec; 11 (4): 769-85
6. Murphy S, Peterson P, Iland H, et al. Experience of the Polycythemia Vera Study Group with essential thrombocythemia: a final report on diagnostic criteria, survival, and leukemic transition by treatment. Semin Hematol 1997 Jan; 34 (1): 29-39
7. Green AR, Vassiliou GS, Curtin N, et al. Management of the myeloproliferative disorders: distinguishing data from dogma. Hematol J 2004; 5 (Suppl.3): S126-132
8. Thiele J, Kvasnicka HM. Chronic myeloproliferative disorders with thrombocythemia: a comparative study of two classification systems (PVSG, WHO) on 839 patients. Ann Hematol 2003; 82: 148-52
9. Florena AM, Tripodo C, Iannitto E, et al. Value of bone marrow biopsy in the diagnosis of essential thrombocythemia. Haematologica 2004; 89 (8): 911-9
10. Rozman C, Giralt M, Feliu E, et al. Life expectancy of patients with chronic nonleukemic myeloproliferative disorders. Cancer 1991; 67: 2658-63
11. Passamonti F, Rumi E, Pungolino E, et al. Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. Am J Med 2004; 117: 755-61
12. Finazzi G, Barbui T. Risk-adapted therapy in essential thrombocythemia and polycythemia vera. Blood Rev 2005; 19: 243-52
13. Barbui T, Barosi G, Grossi A, et al. Practice guidelines for the therapy of essential thrombocythemia: a statement from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation. Haematologica 2004 Feb; 89 (2): 215-32
14. Birgegård G, Björkholm M, Kutti J, et al. Adverse effects and benefits of two years of anagrelide treatment for thrombocythemia in chronic myeloproliferative disorders. Haematologica 2004 May; 89 (5): 520-7
15. Tomer A. Effects of anagrelide on in vivo megakaryocyte proliferation and maturation in essential thrombocythemia. Blood 2002 Mar 1; 99 (5): 1602-9
16. Wang G, Franklin R, Hong Y, et al. Comparison of the biological activities of anagrelide and its major metabolites in haematopoietic cell cultures. Br J Pharmacol 2005 Oct; 146 (3): 324-32
17. Shire US Inc. Citizen Petition re ANDA for anagrelide hydrochloride capsules; docket no. 2004P-0365/CP1 [online]. Available from URL: http://www.fda.gov [Accessed 2005 Nov 9]
18. Mazur EM, Rosmarin AG, Sohl PA, et al. Analysis of the mechanism of anagrelide-induced thrombocytopenia in humans. Blood 1992 Apr 15; 79 (8): 1931-7
19. Tefferi A, Silverstein MN, Petitt RM, et al. Anagrelide as a new platelet-lowering agent in essential thrombocythemia: mechanism of action, efficacy, toxicity, current indications. Semin Thromb Hemost 1997; 23 (4): 379-83
20. Thiele J, Kvasnicka HM, Fuchs N, et al. Anagrelide-induced bone marrow changes during therapy of chronic myeloproliferative disorders with thrombocytosis: an immunohistochemical and morphometric study of sequential trephine biopsies. Haematologica 2003 Oct; 88 (10): 1130-8
21. Dingli D, Tefferi A. A critical review of anagrelide therapy in essential thrombocythemia and related disorders. Leuk Lymphoma 2005 May; 46 (5): 641-50
22. Thiele J, Kvasnicka HM, Ollig S, et al. Anagrelide does not exert a myelodysplastic effect on megakaryopoiesis: a comparative immunohistochemical and morphometric study with hydroxyurea. Histol Histopathol 2005; 20: 1071-6
23. Solberg LA, Tefferi A, Oles KJ, et al. The effects of anagrelide on human megakaryocytopoiesis. Br J Haematol 1997 Oct; 99 (1): 174-80
24. Bellucci S, Legrand C, Boval B, et al. Studies of platelet volume, chemistry and function in patients with essential thrombocythaemia treated with anagrelide. Br J Haematol 1999 Mar; 104: 886-92
25. Laguna S, Correa G, Marta RF, et al. Platelet function and response to anagrelide treatment in essential thrombocythaemia [abstract no. 571]. Haemostasis 1996 Oct; 26 (Suppl. 3)
26. Cacciola RR, Francesco ED, Giustolisi R, et al. Effects of anagrelide on platelet factor 4 and vascular endothelial growth

factor levels in patients with essential thrombocythemia [letter]. Br J Haematol 2004 Sep; 126 (6): 885-6
27. Laguna MS, Kornblihtt LI, Marta RF, et al. Thromboxane B_2 and platelet derived growth factor in essential thrombocythemia under anagrelide treatment (in Spanish). Medicina (B Aires) 2000; 60 (4): 448-52
28. Cacciola RR, Cipolla A, Di Francesco E, et al. Treatment of symptomatic patients with essential thrombocythemia: effectiveness of anagrelide. Am J Hematol 2005; 80: 81-3
29. Laguna MS, Kornblihtt LI, Marta RF, et al. Effectiveness of anagrelide in the treatment of symptomatic patients with essential thrombocythemia. Clin Appl Thromb Hemost 2000 Jul; 6 (3): 157-61
30. Lev PR, Marta RF, Vassallu P, et al. Variation of PDGF, TGFβ, and bFGF levels in essential thrombocythemia patients treated with anagrelide. Am J Hematol 2002 Jun; 70: 85-91
31. Yoon S-Y, Li C-Y, Mesa RA, et al. Bone marrow effects of anagrelide therapy in patients with myelofibrosis with myeloid metaplasia. Br J Haematol 1999 Sep; 106 (3): 682-8
32. Barbui T, Finazzi G. When and how to treat essential thrombocythemia. N Engl J Med 2005 Jul 7; 353 (1): 85-6
33. Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med 2005 Jul 7; 353 (1): 33-45
34. Shire Pharmaceuticals Limited (UK). Xagrid 0.5mg hard capsule prescribing information [online]. Available from URL: http://emc.medicines.org.uk [Accessed 2005 Mar 15]
35. Shire US Inc. Agrylin® (anagrelide hydrochloride) capsules prescribing information. NY: Shire US Inc., 2004 Dec
36. Steurer M, Gastl G, Jedrzejczak W-W, et al. Anagrelide for thrombocytosis in myeloproliferative disorders: a prospective study to assess efficacy and adverse event profile. Cancer 2004 Nov 15; 101 (10): 2239-46
37. James CW. Anagrelide-induced cardiomyopathy. Pharmacotherapy 2000 Oct; 20 (10): 1224-7
38. Jurgens DJ, Moreno-Aspitia A, Tefferi A. Anagrelide-associated cardiomyopathy in polycythemia vera and essential thrombocythemia [letter]. Haematologica 2004 Nov; 89 (11): 1394-5
39. Gaver RC, Deeb G, Pittman KA, et al. Disposition of anagrelide, an inhibitor of platelet aggregation. Clin Pharmacol Ther 1981 Mar; 29 (3): 381-6
40. University of Utah health care hospitals & clinics drug information service. Anagrelide (Agrylin) exposure increased in patients with hepatic impairment, contraindicated in severe hepatic impairment [online]. Available from URL: http://uuhsc.utah.edu/pharmacy/alerts [Accessed 2005 Sep 20]
41. Basara N, Gotic M, Bogdanovic A, et al. Treatment of thrombocythemia with anagrelide: a single institutional experience [abstract no. 288]. Eur J Clin Pharmacol 1997; 52 (Suppl.): A103
42. Kornblihtt LI, Vassallu PS, Heller P, et al. Treatment of essential thrombocythemia with anagrelide: a ten-year experience (in Spanish). Medicina (B Aires) 2002; 62 (3): 231-6
43. Mazzucconi MG, Redi R, Bernasconi S, et al. A long-term study of young patients with essential thrombocythemia treated with anagrelide. Haematologica 2004 Nov; 89 (11): 1306-13
44. Mazur G, Wróbel T, Podolak-Dawidziak M, et al. Anagrelide in the treatment of thrombocythaemia essentialis (ET) (in Polish). Pol Arch Med Wewn 2004 Dec; 112 (6): 1445-50
45. Mills AK, Taylor KM, Wright SJ, et al. Efficacy, safety and tolerability of anagrelide in the treatment of essential thrombocythaemia. Aust N Z J Med 1999 Feb; 29: 29-35
46. Petrides PE, Beykirch MK, Trapp OM. Anagrelide, a novel platelet lowering option in essential thrombocythaemia: treatment experience in 48 patients in Germany. Eur J Haematol 1998 Aug; 61: 71-6
47. Kutti J, Wadenvik H. Diagnostic and differential criteria of essential thrombocythemia and reactive thrombocytosis. Leuk Lymphoma 1996; 22 Suppl. 1: 41-5
48. Storen EC, Tefferi A. Long-term use of anagrelide in young patients with essential thrombocythemia. Blood 2001 Feb 15; 97 (4): 863-6
49. Bennett CL, Weinberg PO, Golub RM. Cost-effectiveness model of a phase II clinical trial of a new pharmaceutical for essential thrombocythemia: is it helpful to policy makers? Semin Hematol 1999 Jan; 36 (1 Suppl. 2): 26-9
50. Golub R, Adams J, Dave S, et al. Cost-effectiveness considerations in the treatment of essential thrombocythemia. Semin Oncol 2002 Jun; 29 (3 Suppl. 10): 28-32
51. Cortelazzo S, Finazzi G, Ruggeri M, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med 1995 Apr 27; 332 (17): 1132-6
52. Harrison CN. Essential thrombocythaemia: challenges and evidence-based management. Br J Haematol 2005; 130: 153-65
53. Najean Y, Rain J-D. Treatment of polycythemia vera: the use of hydroxyurea and pipobroman in 292 patients under the age of 65 years. Blood 1997 Nov 1; 90 (9): 3370-7
54. Finazzi G, Ruggeri M, Rodeghiero F, et al. Efficacy and safety of long-term use of hydroxyurea in young patients with essential thrombocythemia and a high risk of thrombosis [letter]. Blood 2003 May 1; 101 (9): 3749
55. Furgerson JL, Vukelja SJ, Baker WJ, et al. Acute myeloid leukemia evolving from essential thrombocythemia in two patients treated with hydroxyurea. Am J Hematol 1996 Feb; 51 (2): 137-40
56. Weinfeld A, Swolin B, Westin J. Acute leukaemia after hydroxyurea therapy in polycythaemia vera and allied disorders: prospective study of efficacy and leukaemogenicity with therapeutic implications. Eur J Haematol 1994; 52: 134-9
57. Finazzi G, Ruggeri M, Rodeghiero F, et al. Second malignancies in patients with essential thrombocythaemia treated with busulphan and hydroxyurea: long-term follow-up of a randomized clinical trial. Br J Haematol 2000; 110: 577-83
58. Michiels JJ, Van Genderen PJJ. Essential thrombocythemia in childhood. Semin Thromb Hemost 1997; 23 (3): 295-301
59. Passamonti F, Lazzarino M. Treatment of polycythemia vera and essential thrombocythemia: the role of pipobroman. Leuk Lymphoma 2003 Sep; 44 (9): 1483-8
60. Finazzi G, Barbui T. Treatment of essential thrombocythemia with special emphasis on leukemogenic risk. Ann Hematol 1999; 78 (9): 389-92
61. Drugs @ FDA. Vercyte pipobroman [online]. Available from URL: www.accessdata.fda.gov [Accessed 2005 Sep 21]
62. Campbell PJ, Scott LM, Buck G, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet 2005 Dec 3; 366 (9501): 1945-53
63. Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. Br J Haematol 2004; 128: 275-90
64. AOP Orphan Pharmaceuticals AG. AOP 03-007 ANAHYDRET study [online]. Available from URL: http://www.anahydret.at [Accessed 2005 Sep 5]

65. Chintagumpala MM, Steuber CP, Mahoney DH, et al. Essential thrombocythemia in a child: management with anagrelide. Am J Pediatr Hematol Oncol 1991; 13 (1): 52-6
66. Chintagumpala MM, Kennedy LL, Steuber CP. Treatment of essential thrombocythemia with anagrelide. J Pediatr 1995 Sep; 127 (3): 495-8
67. Hankins J, Naidu P, Rieman M, et al. Thrombocytosis in an infant with high thrombopoietin concentrations. J Pediatr Hematol Oncol 2004 Feb; 26 (2): 142-5
68. Hermann J, Fuchs D, Sauerbrey A, et al. Successful treatment of essential thrombocythemia with anagrelide in a child. Med Pediatr Oncol 1998 Jun; 30 (6): 367-70; discussion 370-1
69. Lackner H, Urban C, Beham-Schmid C, et al. Treatment of children with anagrelide for thrombocythemia. J Pediatr Hematol Oncol 1998 Sep; 20 (5): 469-73

Correspondence: *Antona J. Wagstaff*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz