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Adverse effects and benefits of two years of anagrelide treatment for thrombocytopenia in chronic myeloproliferative disorders

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A B S T R A C T

Background and Objectives. Although anagrelide is widely used in the treatment of thrombocytopenia in myeloproliferative diseases, there is currently limited information on the efficacy and toxicity of its long-term use. This prospective study investigated clinical toxicity and efficacy of anagrelide during two years of treatment.

Design and Methods. A multicenter, open, phase II study of anagrelide treatment was performed by the Swedish Myeloproliferative Disorder Study Group. The study included 60 patients with thrombocytopenia due to myeloproliferative disease, 42 with essential thrombocytopenia (ET), 17 with polycythemia vera (PV) and one with myelofibrosis (MF).

Results. Complete response (CR), defined as a platelet count $<400 \times 10^9/L$ in symptomatic patients and $<600 \times 10^9/L$ in asymptomatic patients was achieved in 67% of the patients and partial response (PR) in 6%. The response rate was higher in patients with ET than in those with PV ($p = 0.05$). Primary treatment failure occurred in 27% due to lack of efficacy at a tolerable dose ($n=13$) or insufficient platelet response without side effects ($n=3$). In addition, another 14 patients withdrew from treatment before the end of the two-year period due to side effects. Side effects included palpitations (70%), headache (52%), nausea (35%), diarrhea or flatulence (33%), edema (22%) and fatigue (23%). Patients and doctors rated their satisfaction with the anagrelide treatment on a 10-grade scale from 7.6 at 3 months to >9 at 24 months. After two years, 50% ($n=30$) of the patients continued anagrelide treatment.

Interpretation and Conclusions. Side effects and toxic discontinuation rates were higher than in previous studies, probably because this is the first long-term prospective study of the feasibility and toxicity of anagrelide treatment. Nevertheless, anagrelide is a valuable alternative for treatment of thrombocytopenia in myeloproliferative disorders for patients who tolerate the drug well.

Key words: thrombocytopenia, anagrelide, myeloproliferative disease.

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The chronic myeloproliferative disorders (MPD) are a group of related diseases that are characterized by neoplastic proliferation in one or more hematopoietic cell lines.

One of the most prevalent clinical challenges in the treatment of myeloproliferative disorders is thrombocytopenia, which is always present in essential thrombocytopenia (ET) and may also occur in the other disorders. The hazards associated with thrombocytopenia are thromboembolic incidents as well as bleeding. There is no consensus concerning the trigger level for platelet-lowering therapy and there is, understandably, a lack of controlled studies. Many clinicians have chosen a platelet limit around $1000 \times 10^9/L$ as a trigger level, while others have chosen $1500 \times 10^9/L$. However, factors such as previous thromboembolic incidents and age increase the risk for

thrombosis so that a risk classification system has been widely accepted that uses platelet numbers, age and previous history as risk criteria.¹⁻³ The Swedish national working group for myeloproliferative disorders has issued guidelines for therapy, stating that a platelet level of $1000 \times 10^9/L$ should be used as the trigger level for treatment, with the addition that patients with a previous history of thromboembolic events, ongoing signs of thromboembolism or microcirculatory symptoms should be treated when the platelet level is $>600 \times 10^9/L$.

At present, the main options for platelet reducing therapy are hydroxyurea (HU), α -interferon (IFN) and in some countries pipobroman, this last, however, not being available in Nordic countries. Busulphan and radioactive phosphorus (P32) are now rarely used, and particularly not in essential thrombocytopenia. The suppressive effect on

all cell lineages in the bone marrow may be an advantage in polycythemia vera if there is a hyperproliferative erythropoiesis, but is a problem in the presence of anemia and/or leukopenia. There is general agreement that P32 gives rise to secondary malignancies.⁴ There is still controversy concerning hydroxyurea; studies showing an increased frequency of leukemia have been criticized for bias, due to the fact that patients with more aggressive disease are more likely to receive cytostatic treatment. However, there is increasing concern about the possible long-term leukemogenic effect of hydroxyurea,⁵ especially when used in patients who have also received busulphan treatment.^{6,7} Hydroxyurea also causes skin lesions in a number of patients, and α -interferon is associated with a rather high incidence of side effects in the central nervous system such as fatigue and depression, which result in drop-out rates of about 25% among treated patients.^{8,9}

Given the relatively high incidence of adverse events that are experienced with the clinically available platelet-reducing agents, there is a great need for alternatives, and the platelet-reducing agent anagrelide is an addition to the therapeutic arsenal. Anagrelide is not a cytostatic drug, and its effect is selective and limited only to the megakaryocyte cell lineage. Anagrelide reduces platelet production by inhibiting megakaryocyte colony development, thereby reducing megakaryocyte size, ploidy, and disrupting or preventing full megakaryocyte maturation. These effects appear to occur in the non-mitotic, late stages of megakaryocyte development¹⁰ and have been confirmed in *in vivo* studies.^{11,12} The thrombocytopenic effect of anagrelide appears to be species-specific for humans, and has not been reproduced in experimental animal models, a finding that has limited the study of the pharmacodynamic properties of this drug.

The platelet-reducing effect of anagrelide is well documented. Since the first study published in 1992,¹³ anagrelide has been evaluated in a number of investigations.¹⁴⁻¹⁹ However, the long-term feasibility of treatment in clinical practice is yet to be evaluated. The only long-term report on anagrelide treatment (over a 10-year period) was retrospective¹⁸ and all other studies evaluating toxicity were either short-term or retrospective. Toxic drop-out rates and side effects are difficult to evaluate in retrospective studies. The most common adverse events are headache, nausea, diarrhea, palpitations and edema. It has been claimed that side effects are mild and mainly experienced early in the treatment.

Since no prospective, long-term study of feasibility and toxic effects has been published so far, we conducted a non-randomized study in 60 patients to investigate long-term tolerance, feasibility and toxicity of anagrelide treatment over a two-year time period. The

Table 1. Diagnoses and gender distribution (n;%).

Diagnosis	Females	%	Males	%	Total	%
ET	27	77	15	60	42	70
PV	8	23	9	36	17	28
MF	0	0	1	4	1	2
Total	35	100	25	100	60	100

ET: essential thrombocythemia; PV: polycythemia vera; MF: myelofibrosis.

frequency of thromboembolic complications or deaths were not the main focus of this study, since the numbers of these events are expected to be small and it would not be possible to draw firm conclusions from a non-randomized study in this respect.

Patients

This was a prospective, open label, multicenter, non-comparative phase II clinical trial including 60 patients with a diagnosis of myeloproliferative disease, 17 with polycythemia vera (PV), 42 with essential thrombocythemia (ET) and 1 with myelofibrosis (MF) (Table 1) and a platelet count $> 600 \times 10^9/L$ in symptomatic patients or $> 1\,000 \times 10^9/L$ in all other patients at repeated measurements. Symptoms were defined as previous thromboembolic episodes or ongoing microcirculatory symptoms. The diagnosis was established according to the diagnostic criteria of Pearson *et al.* for polycythemia vera¹ or Kutti and Wadenvik¹⁹ for essential thrombocythemia. Patients with cardiac failure (New York Heart Association classification grade II-IV) or clinically significant cardiac arrhythmia were not included.

The mean age of the whole group was 52.7, median 53.5 (27-75) years. The mean age of the females was 4 years lower than that of the males, the median being 7 years lower (50 versus 57). Thirty-three patients had had no previous treatment, 21 patients had received hydroxyurea alone, 4 patients had received interferon alone, one patient had received hydroxyurea + interferon, and one patient had received hydroxyurea + busulphan.

The study was designed to assess the feasibility of anagrelide treatment, i.e. clinical effects, short- and long-term tolerability and patients' management, in patients with thrombocythemia due to chronic myeloproliferative disorders, treated with anagrelide to reach pre-set goals of platelet levels, defined as platelets $< 600 \times 10^9/L$ for asymptomatic patients and $< 400 \times 10^9/L$ for symptomatic ones.

Treatment

The decision to treat conformed with the Swedish national recommendations for patients with myeloproliferative disease. Patients who previously had fulfilled platelet inclusion criteria and who were under treat-

ment with another agent to control platelets were switched over to anagrelide. The previous medication was discontinued long enough to ascertain that platelet numbers had begun to increase before anagrelide was instituted. Anagrelide was administered orally. The starting dose was 0.5 mg given twice a day. If there was no response the daily dose was increased by 0.5 mg each week. The dose limit was 2.5 mg for a single dose and 8 mg/day. If the dose exceeded 3 capsules/day, patients were encouraged to spread the intake over three or four occasions. Patients were evaluated weekly until the dose had been adjusted to the lowest effective dose required to reduce and maintain a platelet count $< 400 \times 10^9/L$ in symptomatic patients or $< 600 \times 10^9/L$ in asymptomatic patients. The intended treatment duration was two years.

Complete response was defined as a platelet count $< 400 \times 10^9/L$ or $< 600 \times 10^9/L$ in symptomatic and asymptomatic patients, respectively, for at least 4 weeks. Partial response was defined as a reduction of the platelet count to at least 50 % of the baseline value. Treatment failure was considered to be a platelet count that did not fall below < 50 % of the baseline value. Twenty-eight patients received continuous treatment with 75 mg of aspirin daily during the study.

Design and Methods

Side effects were recorded at monthly follow-up assessments during the first 3 months and then every 3 months, and graded I-IV according to the WHO grading scale. Both patients and doctors evaluated the anagrelide treatment using a 10-point visual analog scale consisting of a single global question (Figure 4) at 3, 6, 12 and 24 months. The patients were asked by the doctor to indicate on the 10-grade visual analog scale to what degree they endorsed the global statement *I think Agrylin treatment works well for me*. After the visit, the doctor did the same for the statement *I think Agrylin treatment works well for this patient*. The patients were asked to include all aspects of the treatment, including effect, side effects, blood sampling and dose changes. The doctors, likewise, were asked to include all management aspects, including efficacy, side effects and ease of monitoring.

Blood counts were performed routinely in the hospital clinical chemistry laboratories.

Statistical methods

Changes in hemoglobin (Hb) levels were tested with Wilcoxon test for two-sided significance, and the correlation between anagrelide dose and Hb lowering was tested with the Pearson product moment correlation test. The Mann-Whitney U-test was used to compare

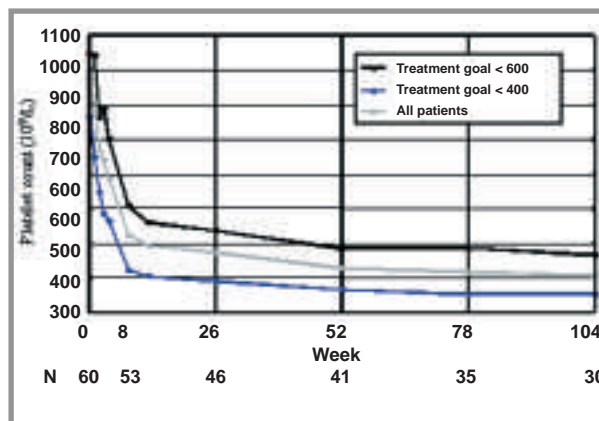


Figure 1. Platelet-lowering effect of anagrelide treatment. Mean curves for all patients.

dose levels in patients who responded to the treatment and those who did not.

Results

The overall response rate was 73% (67% complete responses, 6% partial responses); the failure rate was 27%. The mean time to complete response was 1.5 (median 1, range 0.5-5) months. Primary treatment failure was usually due to lack of efficacy at a tolerable dose. There was no significant difference in efficacy between genders, but a higher response rate was observed in essential thrombocythemia (76%) than in polycythemia vera (41%), $p = 0.05$ (Figures 1 and 2). In patients with an insufficient platelet lowering effect who had no side effect problems, the treatment was stopped after 3.2 ± 1.4 (mean \pm SD) months.

In addition to the 16 primary failures, another 14 patients withdrew from treatment before the end of the two-year period. The most common reasons for stopping treatment were lack of efficacy at a tolerable dose ($n=13$), and side effects while in CR ($n=10$) (Table 2). The mean time to drop-out was 8.9 ± 2.2 months and 11.4 ± 2.7 months for the categories "lack of effect at tolerable dose" and "side effects but CR", respectively.

The patients who had a complete response and tolerated the drug needed few dose changes after reaching their maintenance dose, with an average of one dose change per 3 months. There were 3 short-term treatment interruptions due to platelet reduction in excess of the treatment goal, but no platelet value below the reference range was recorded. The dose increase schedule described in the protocol was followed carefully. At no time did the dosage exceed the stipulated limits of 2.5 mg per dose. In addition, the maximal daily dose was 5 mg and the minimum 0.5 mg. The maintenance dose was around 2.2 mg/day, and

Table 2. Reasons for discontinuing anagrelide treatment.

Reasons for stopping treatment	
Insufficient effect at tolerable dose	13
Side effects (but CR)	10
Insufficient effect, no side effects	3
Non-compliance	1
Other treatment interventions	3
Total	30

there was no increase in mean dose over time (Table 3). There was no significant difference in dose administered to the ET or PV patients ($p = 0.3$).

Side effects included palpitations (70%), headache (52%), nausea (35%), diarrhea or flatulence (33%), edema (22%) and fatigue (23%) (Figure 3). The frequency and severity of side effects was dose-dependent. In many cases there was a trade-off between the wish to increase the dose in order to achieve platelet response and the increase in the severity of the side effects observed. This is illustrated by the fact the mean last dose before stopping treatment in patients who had an insufficient effect at a tolerable dose ($n=13$) was significantly higher than the maintenance dose in patients who continued treatment (2.6 versus 2.3 mg/day, $p = 0.05$).

A majority of the side effects were of WHO grade I or II, but a number of patients had grade III side effects, most notably severe headache or diarrhea. One patient lost 7 kg of body weight due to 7–8 loose stools daily for 2 weeks. Another patient developed pronounced peripheral edema (grade IV). There were no significant differences in frequency or severity of side effects between patients with ET or PV.

Patients and doctors rated the feasibility of anagrelide treatment on the 10-grade scale (Figure 4) from 7.6 at 3 months to >9 at 24 months. The patients who continued treatment for the full 2 years ($n=30$) showed a high degree of satisfaction, as did their doctors.

Table 3. Mean anagrelide doses did not need to be increased after the first 3 months.

Time	2 weeks	3 months	6 months	12 months	18 months	24 months
Anagrelide dose Mean \pm SD	1.03 \pm 0.13	2.33 \pm 0.16	2.36 \pm 0.15	2.31 \pm 0.15	2.17 \pm 0.16	2.20 \pm 0.16

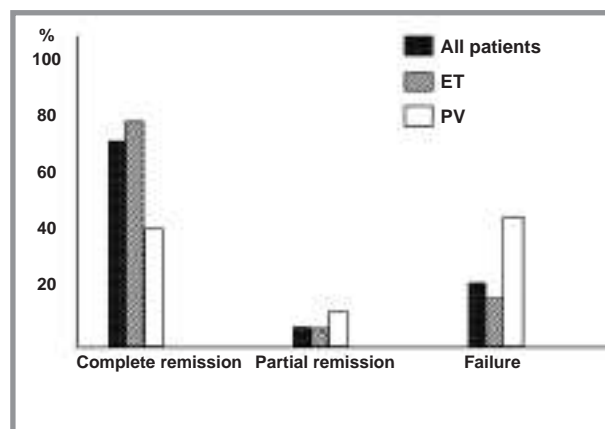


Figure 2. Platelet response to anagrelide therapy. The response rate was higher in essential thrombocythemia, failures more common in polycythemia vera. ET: essential thrombocythemia; PV: polycythemia vera.

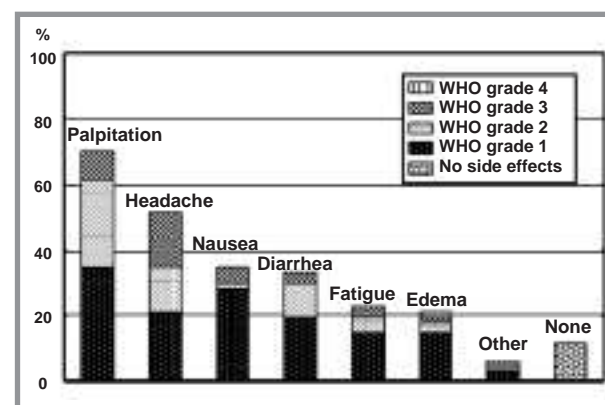


Figure 3. Frequency and severity of side effects. For each patient the worst rating during the study for the various side effects is reported.

The Hb level dropped significantly during treatment, this effect first occurring within one week after the initiation of treatment ($p = 0.002$). The mean initial Hb level was 13.2 \pm 0.2 g/dL, and the lowest mean Hb was 12.7 \pm 0.3 g/dL in week 8. Seven patients had a Hb value more than 2 g/dL lower than their initial level at some time during the first 8 weeks. The mean Hb level during the whole study was significantly (13.2 versus 12.7–12.9 g/dL) lower than the initial value (Figure 5). There was a negative Pearson correlation coefficient

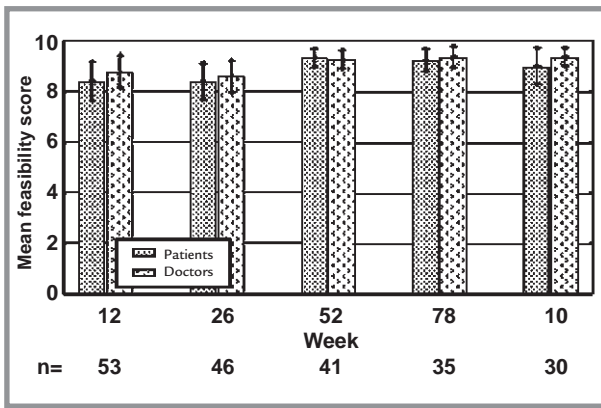


Figure 4. Feasibility rating. Patients and doctors rated anagrelide treatment on a 10-grade scale according to their level of agreement with the global statement *I think anagrelide treatment works well for me and I think anagrelide treatment works well for this patient, respectively.* (Mean \pm SD).

between Hb level and anagrelide dose for all weeks tested ranging from -0.09 to -0.3 , $p = 0.003$ for all weeks.

Adverse events leading to hospitalization

Thromboembolic events occurred during the study in two patients, who both had a CT-verified cerebral infarction. Their platelet levels were 433 and $247 \times 10^9/L$, at the time of the event. One of these patients had polycythemia vera, the other had essential thrombocythemia. A third patient, with polycythemia vera, had a myocardial infarction at a platelet level of $430 \times 10^9/L$. These three patients all had a Hct $< 45\%$ at the time of the event. All three were over 70 years of age, and none of them had had a previous thromboembolic episode.

One patient was hospitalized for chest pain without signs of myocardial infarction, two patients had vertigo leading to hospital care. One of these had a platelet level of $1,000 \times 10^9/L$ after stopping anagrelide treatment on his own initiative due to insomnia. One patient, who had previously had problems of mild heart failure, was hospitalized twice for worsening cardiac failure, after which the drug was stopped. Another patient was admitted to hospital for a few days because of diarrhea and abdominal pain.

There was one case of severe nephritis. The patient was a 75-year old farmer with polycythemia vera diagnosed in 1992, who had been treated with hydroxyurea from 1995 to May 1999. Anagrelide treatment ($0.5 \text{ mg} \times 2$) was started on August 4, 1999. Pretreatment laboratory evaluation included a serum creatinine of 136 mmol/L and a C-reactive protein concentration of 100 mg/L . Three days later the patient developed nausea and vomiting (initially thought to be caused by food intolerance or an innocent gastrointestinal infection) and slight fever. When the patient recovered from this episode two

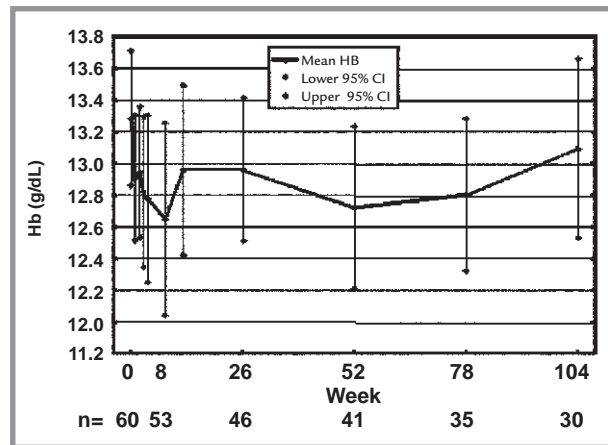


Figure 5. Mean Hb curve for all patients. A significant reduction of the Hb level was seen after one week and remained throughout the study.

days later, the anagrelide dose was increased to $0.5 \text{ mg} \times 3/\text{day}$, and to $0.5 \text{ mg} \times 4$ on August 18. Around August 20 the patient's general condition deteriorated, resulting in hospitalization on August 23. At this point the patient was clearly uremic with a serum creatinine of $1,300 \text{ mmol/L}$. A renal biopsy on August 25 showed typical tubulointerstitial nephritis.

Hemodialysis was initiated the same day and repeated at intervals of 2-3 days. The patient was started on corticosteroids. Improvement occurred rapidly but the serum creatinine remaining elevated for several months, before eventually normalizing completely.

Discussion

The main finding of this study is that anagrelide treatment induces more side effects during long-term use than had been previously reported. Even though side effects did, to some extent, abate during the first months of therapy, as described in previous studies, a large number of patients still experienced the same intensity of side effects after several months of treatment, as indicated by the long mean drop-out time. As many as 50% of the patients stopped the treatment within two years, most of them due to severe side effects which either significantly decreased the patient's quality of life and/or made it impossible to increase the dose if adequate platelet reduction was not achieved. Some patients tried to endure the side effects because the platelet level obtained was satisfactory but finally had to stop treatment. The most common and severe side effects were headache, palpitations and diarrhea. Even though anagrelide is a vasodilator at high doses and has a positive inotropic activity, which is probably responsible for the forceful

heartbeat and/or tachycardia occurring in some patients, there is no evidence that the drug causes significant arrhythmias. In the current study one patient, who was already on maintenance treatment for mild heart failure experienced two episodes of heart failure symptoms during the treatment period. As a result, anagrelide administration was stopped. Anagrelide has been used with caution in patients with known or suspected heart disease and, given our results, this seems warranted.

The episode of severe nephritis was judged by independent nephrologists as very probably being a side effect of anagrelide, since no other cause could be found and the condition subsided when anagrelide treatment was terminated. Previous cases of renal failure with a possible relationship to anagrelide have been reported. Out of 15 cases of renal insufficiency during anagrelide treatment, 11 had pre-existing renal disease, but 4 were *de novo* cases.²¹ One of the patients in the current study had biopsy-verified interstitial nephritis with fever and liver dysfunction 14 months after the end of the study (after 3 years and 2 months of treatment). The peak creatinine level of 200 mmol/L normalized after cessation of anagrelide, but mild hypertension is still present a year later. The mechanism for a possible causal relationship between anagrelide therapy and renal damage is unknown, but caution is clearly indicated, especially in patients with pre-existing renal disease.

The higher frequency and severity of side effects recorded in the current study than in previous studies are most likely due to the fact that this was a prospective feasibility and toxicity study, whereas most other studies have been efficacy studies with focus on the platelet-lowering effect of anagrelide and/or have been retrospective surveys. Retrospective evaluation of side effects from studies in which toxicity assessment is not a primary objective are of limited value, since spontaneously recorded toxicity often gives an underestimate of the true frequency and severity. Likewise, the drop-out rate due to side-effects must be studied in a prospective manner. One smaller prospective study showed a drop-out rate due to side effects that was similar to the rate in this study, with 37% of patients dropping out within the first 7 months.¹⁹ Nevertheless the authors claimed that side effects were a minor problem and resolved in most cases. In a recent study¹⁷ in 22 patients a lower frequency of side effects and a lower drop-out rate were noted, but the mean dose of anagrelide given in that study was also much lower, 1.4 mg/day, compared with the 2.3 mg in our and other studies. The reason for this is unclear, but possible explanations may include: a lower entrance platelet level (median $550 \times 10^9/L$), a small number of patients, inclusion of more patients with essential thrombo-

cythemia relative to polycythemia vera (19/22), and shorter study period (2 to 25 months, median 8 months). In addition, in at least one case combination therapy was allowed. The platelet response rate in our study was comparable to that in most other studies, being around 70%. It should be noted that the response rate was higher among patients with essential thrombocytopenia than among those with polycythemia vera.

The patients who were still on treatment after two years (50% of the total patient population) had a good and sustained effect of the drug and either no or relatively mild side effects. The platelet lowering effect of the drug did not decrease during the study period, indicating that this agent may be useful for cases when long-term therapy is anticipated. In addition, after the initial 3 months, the mean dose did not increase over the two years. Dose changes were not necessary more than every third month (mean), and no patient had a subnormal platelet count as a result of treatment. There were only two temporary treatment interruptions because of platelet levels sinking below the treatment goal. These results indicate that anagrelide has a good feasibility profile for patients who do not suffer from side effects.

Both doctors and patients showed a high degree of satisfaction with the treatment, especially during the latter part of the study, when those patients with many side effects had left the study. The first measurement on the feasibility scale was made at three months after the onset of treatment in order to show the maintenance situation. Nevertheless, there were still a number of patients on treatment at 3 and 6 months who had considerable side effects but wished to continue treatment. This is probably why the feasibility scores improved after 6 months. It is interesting to note the discrepancy between the fairly high feasibility scores and the frequency and severity of reported side effects as well as the similarity in scores between patients and doctors. A number of patients with grade II palpitations or headache still rated treatment feasibility above 9, as did their doctors. It is possible that the global instrument used had a low sensitivity and that a placebo effect increased the scores. The satisfaction of the doctors was probably partly due to the fact that the drug was easy to handle; there were no cases with subnormal platelet levels and only a few short treatment interruptions.

It is quite possible that more patients would have responded well to anagrelide, with a lowering of the platelets to the treatment goal, if the dose could have been increased. However, side effects were clearly dose-dependent, and in many cases a dose increase was impossible because of one or more of the major side effects: palpitations, headache or loose stools/diarrhea.

The 10 patients who were classified as complete

responders but later stopped treatment due to side effects were basically not different from the 13 classified as having *lack of efficacy at tolerable dose* but went into complete response because they tolerated a higher degree of side effects for some time before they had to discontinue therapy. The clinical reason for switching patients from other treatments to anagrelide is often either intolerance or lack of effect. In patients who have problems tolerating anagrelide at a dose sufficiently high to give an adequate platelet response it seems logical to use a combination with other drugs, so that both doses and side effects could be minimized. However, so far only one published study has explored this possibility.²² There was a significant but low-grade decrease of the Hb level, which has been found in two previous studies^{18,23} and has been ascribed to the vasodilatation produced by anagrelide. The fact that in the current study a significant decrease of the mean Hb level was present already after 1 week of treatment supports this hypothesis, since it would probably be too early to be the effect of bone marrow inhibition. It is interesting to note that the Hb lowering effect, whether caused by vasodilatation or not, was persistent during the two years but did not progress. The degree of Hb lowering was dose-dependent, indicating that there is a causal relationship. Twenty-three percent of the patients reported fatigue, mostly grade I during treatment. Fatigue could be a central nervous system effect of the drug or could perhaps be mediated through anaemia. However, there was no correlation between the degree of Hb decrease and reported fatigue, and a decrease of Hb was not more common or severe in patients who reported fatigue.

The number of thrombotic events (n=3) was low, as expected. It is still unclear whether anagrelide reduces the risk of thrombotic events, and this study was not designed to answer this question. A European multicenter study was stopped after an interim analysis showing a larger number of hemorrhagic complications in the experimental group being treated with

anagrelide + aspirin than in the control group receiving hydroxyurea + aspirin. However, in our study no hemorrhagic complications were seen, although almost half of the patients were receiving continuous aspirin treatment. None of the patients had any clinical deterioration during the study. The effect of anagrelide treatment on biological markers, including marrow fibrosis, is under investigation and will be reported separately.

Anagrelide, at tolerable doses, was effective in reducing platelets in 67% of patients with myeloproliferative disorders. However, the total drop-out rate was 50 % over the two-year period with the main causes for dropping out being either insufficient response at tolerable doses or toxic side-effects but adequate platelet lowering effect. The side effects and drop-out rates are higher than those reported in some previous studies. The main reason for this discrepancy is probably that this is the first prospective long-term study designed specifically to evaluate the feasibility of treatment with anagrelide as a single agent. However, for those patients with low-grade or no side effects the drug was appreciated by both patients and doctors for the stability of platelet levels and ease of handling. Our results indicate that anagrelide is a valuable addition to the options for platelet-lowering therapy. The dose dependency of side effects makes it probable that combining anagrelide with other platelet-reducing drugs could be useful.

The design of the study was planned by the authors, all members of the Swedish Myeloproliferative Study Group, within that framework. Dr Birgegård was the principal investigator and was responsible for drafting and revising the study protocol after input from all authors. All authors recruited and treated patients in the study. All authors, and in particular Dr. Jan Samuelsson, revised the manuscript and interpreted the data. All authors approved the version to be published. All authors reported no potential conflicts of interest.

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