26996

USE OF PAF-ANTAGONISTS FOR TREATING AUTOIMMUNE DISEASES

ABSTRACT

The invention relates to the use of PAF-antagonists for treating autoimmune diseases.

This invention relates to the use of PAF-antagonists for treating autoimmune diseases.

In idiopathic thrombocytopenic purpura (ITP), a disorder of the immune mechanism causes massive destruction of the body's own thrombocytes, which are finally eliminated in the spleen. The thrombocyte survival time, instead of being 10 days, is frequently only a few hours and the megacariocytes in the bone marrow which form the thrombocytes are multiplied in compensation.

Previously, this disease was fatal in 60-80% of cases. Since therapy with steroids, particularly prednisolon, the prognosis for ITP has improved significantly.

With this syndrome it is essential in many cases for the therapy, i.e. the drug treatment, to be maintained throughout the patient's life. The disadvantages of long-term cortisone therapy are well known to those skilled in the art.

According to one aspect of the invention, we have found that surprisingly, PAF-antagonists (PAF-acether antagonists) may be used successfully in therapy for treating autoimmune diseases, particularly idiopathic thrombocytopenic purpura, without giving rise to the known side effects of steroid treatment.

Many of the compounds which are used as PAF-antagonists (PAF = platelet activating factor) which may be used according to the invention are known from the patent literature and the specialist literature, e.g. in Prostaglandins 35, 781 (1988).

Examples of known PAF-antagonists include the tetrahydrofuran derivatives SDZ 63-441, SDZ 63-675, L 659.886. BN 52 111, thiazole derivatives of the type RP 59 227, imidazo[2,1-a]-isoquinolines of the type SDZ 64412 and SDZ 63135, dihydro-pyridines, compounds of type SRI 63441, RO 19-3704, CV 6209 and hetrazepine compounds such as thienodiazepines and benzodiazepines. Preferably, PAF-antagonists according to European Patent Applications 194 416 and 254 245, published on September 17, 1986 and January 27, 1988, respectively, may be used according to the invention. The compounds listed below are particularly preferred.

[4-(2-chlorophenyl)-1-methyl-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-carboxylic acid morpholide

[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-carboxylic acid amide

2-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-ethane-1-carboxylic acid diethyl-amide

2-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-ethane-1-carboxylic acid N,N-di-(2-hydroxyethyl)amide

2-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-ethane-1-carboxylic acid methylamide

2-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-ethane-1-carboxylic acid isopropylamide

2-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-ethane-1-carboxylic acid dimethyl-amide

2-[4,(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-ethane-1-carboxylic acid N'-methyl-piperazide

2-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-ethane-1-carboxylic acid pyrrolidide

2-[4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-ethane-1-carboxylic acid piperidide

2-[4-(2-chlorophenyl)-6H-thieno[3,2-f] [1,2,4]triazolo[4,3-a]-[1,4]diazepin-2-yl]-ethane-1-carboxylic acid morpholide

2-[4-(2-chlorophenyl)-9-bromo-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-ethane-1-carboxylic acid morpholide

2-[4-(2-chlorophenyl)-9-methoxy-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepin-2-yl]-ethane-1-carboxylic acid morpholide

4-(morpholin-4-yl-carbonyl)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]diazepine

3-(morpholin-4-yl-carbonyl)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]-diazepine

3-(N,N-diethylaminocarbonyl)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

4-(N,N-diethylaminocarbonyl)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

4-(4-methylpiperazinylcarbonyl)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

4-(N-methyl-N-2-hydroxyethylaminocarbonyl)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]-triazolo[4,3-a] [1,4]diazepine

4-(N,N-dimethylaminocarbonyl)-5-(2-chlorophenyl)-10-methyl-3,4-dihydro-2H,7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

3-(N,N-diethylaminocarbonyl)-5-(2-chlorophenyl)-10-methyl-3,4-dihydro-2H,7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

3-(N,N-diethylaminocarbonyl-5-(2-chlorophenyl)-10-bromo-3,4-dihydro-2H,7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

4-(morpholin-4-yl-carbonylmethylaminocarbonyl)-5-(2-chlorophenyl)-10-bromo-3,4-dihydro-2H,7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]-triazolo[4,3-a] [1,4]diazepine

4-(morpholin-4-yl-carbonyl)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f]imidazo[1,2-a] [1,4]-diazepine

4-(N,N-diethylamino)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f]imidazo[1,2-a] [1,4]diazepine

3-(N-morpholinomethyl)-5-(2-chlorophenyl)-10-methyl-3,4-dihydro-2H,7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]diazepine

3-(acetoxymethyl)-5-(2-chlorophenyl)-10-methyl-3,4-dihydro-2H, 7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]-diazepine

3-(1,2,4-triazolyl-1-yl-methyl)-5-(2-chlorophenyl)-10-methyl-3,4-dihydro-2H,7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

3-(N-2,6-dimethylmorpholino-methyl)-5-(2-chlorophenyl)-10-methyl-3,4-dihydro-2H,7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

3-acetoxymethyl-5-(2-chlorophenyl)-3,4-dihydro-2H,7H-cyclopenta-[4,5]thieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]diazepine

4-acetoxymethyl-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetra-hydro-8H-[1]benzothieno[3,2-f]imidazo[1,2-a] [1,4]diazepine

3-acetoxymethyl-5-(2-chlorophenyl)-10-methyl-3,4-dihydro-2H, 7H-cyclopenta[4,5]thieno[3,2-f]imidazo[1,2-a] [1,4]diazepine

3-diethylaminomethyl-5-(2-chlorophenyl)-10-methyl-3,4-dihydro-2H,7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]diazepine

4-hydroxymethyl-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]diazepine

4-(N-morpholinomethyl)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]diazepine

4-(pyrazolyl-1-yl-methyl)-6-(2-chlorophenyl)-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]diazepine

4-[4,4-dimethyl-2-oxazolin-2-yl]-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

4-[4,4-dimethyl-2-imidazolin-2-yl]-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

4-[1,4,4-trimethyl-2-imidazolin-2-yl]-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]-triazolo[4,3-a] [1,4]diazepine

4-aminocarbonyl-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo[4,3-a]-[1,4]diazepine

4-[morpholin-4-yl-carbonyl]-6-(2-chlorophenyl)-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f]imidazo[1,5-a] [1,4]diazepine

4-[4,4-dimethyl-2-thiazolin-2-yl]-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine

4-amino-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]diazepine

3-(N-morpholinyl-methyl)-5-(2-chlorophenyl)-10-methyl-3,4-dihydro-2H,7H-cyclopenta[4,5]thieno[3,2-f]imidazo[1,2-a]-[1,4]diazepine

4-(1,2,4-triazol-1-yl-methyl)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f] [1,2,4]triazol-[4,3-a] [1,4]diazepine

4-(1,2,4-triazol-1-yl-methyl)-6-(2-chlorophenyl)-11-methyl-2,3,4,5-tetrahydro-8H-[1]benzothieno[3,2-f]imidazo[1,2-a] [1,4]diazepine

The following are more particularly preferred:

6-(2-chlorophenyl)-8,9-dihydro-1-methyl-8-[(4-morpholinyl)-carbonyl]-4H,7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine (Web 2170)

4-(2-chlorophenyl)-9-methyl-2-[3-(4-morpholinyl)-3-propanon-1-yl]-6H-thieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]diazepine (Web 2086)

6-(2-chlorophenyl)-8,9-dihydro-1-methyl-8-[dipropylamino-carbonyl]-4H,7H-cyclopenta[4,5]thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine (Web 2347).

Any reference herein to PAF antagonists includes within its scope all pharmaceutically acceptable acid addition salts thereof, and any and all isomers and tautomers thereof having similar activity.

According to another aspect of the invention we provide a method of treating autoimmune diseases especially idiopathic thromocytopenic purpura in a human or animal subject which comprises administering to the said subject an effective amount of a PAF-antagonist as hereinbefore described.

By way of Example of the application of the invention, a 52 year old male patient with ITP was treated with the PAF-antagonist Web 2086 {4-(2-chlorophenyl)-9-methyl-2-[3-(4-morpholinyl)-3-propanon-1-yl]-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine} in a dosage of 4 x 20 mg a day, by oral route, instead of prednisolon. There was a rapid increase in the thrombocytes which had previously not been observed in the patient in question in the 3 years he had had the disease, reliably diagnosed, during his treatment with steroids. The treatment with Web 2086 was discontinued after 10 days, and there was a corresponding fall in the thrombocyte count, as expected. This is illustrated graphically in Fig. 1, as described below.

The advantage of treatment with PAF-antagonists according to the invention consists in the total absence of side effects,

as far as is currently known in humans, compared with the therapeutic agents hitherto used for this treatment, which have been shown to have considerable side effects, and the rapid increase in the thrombocytes. For a single dose, a dosage range of between 5 and 50 mg for oral administration appears to be acceptable whilst for intravenous administration single doses of between 2.5 and 30 mg are advisable.

In another embodiment according to the invention, the PAF-antagonist may be used in conjunction with a cofactor in a low-dose form. Examples of possible cofactors include substances with an immune suppressant effect as well as steroids in low concentrations.

It is known from prior art that immunosuppressive substances, for example cyclosporin, are recommended for the treatment of idiopathic thrombocytopenic purpura. As is known, cyclosporins give rise to strong side effects. The use of a compound according to the invention has been found to lead to a considerable reduction of these side effects. In this connection, special note has to be taken of the pharmaceutical compositions consisting of a PAF-antagonist, selected from European Patent Applications 176 928, 268 242, 230 942, 240 899, 194 416, 254 245, and 255 028, and a cyclosporin, in particular cyclosporin A, azathioprin or prednisolon. The European Patent Applications listed above contain, as their central structural element, a thieno[3,2-f]-[1,2,4]triazolo-[4,3-a] [1,4]diazepine or a [1,2,4]triazolo-[4,3-a] [1,4]-benzodiazepine. Agents containing the PAF-antagonists Web 2086, Web 2170 or Web 2347 and a cyclosporin, particularly cyclosporin A, are of special significance.

Because of the aetiology of ITP (Werlhof disease) as an autoimmune disease, treatment with PAF-antagonists, particularly 4-(2-chlorophenyl)-9-methyl-2-[3-(4-morpholinyl)-3-propanon-1-yl]-6H-thieno[3,2-f] [1,2,4]triazolo[4,3-a] [1,4]diazepine (Web 2086), may also be advisable in the following autoimmune diseases: autoimmune haemolytic anaemia, autoimmunologically caused glomerulonephritis, thyreoidis Hashimoto, primary myxoedema, pernicious anaemia, autoimmune atrophic gastritis, Addison's disease, juvenile diabetes, Goodpasture syndrome, idiopathic leucopenia, primary biliary cirrhosis, active or chronically aggressive hepatitis (HBsAg-neg.), ulcerative colitis, chronic polyarthritis and systemic lupus erythematodes (SLE).

The synthesis of 4-(2-chlorophenyl)-9-methyl-2-[3-(4-morpholinyl)-3-propanon-1-yl]-6H-thieno[3,2-f] [1,2,4]triazolo-[4,3-a] [1,4]diazepine (Web 2086) and the production of galenic preparations is known from German Offenlegungsschrift DE A1 35 02 392 (Example 1). The synthesis of Web 2170 and Web 2347 is known from European Patent Application 254 245. The active substances may be used in the form of conventional galenic preparations such as tablets, suppositories or injectable solutions. Details of the preparation thereof are disclosed in European Patent Applications 194 416 and 254 245, to which reference is hereby made.

According to a further aspect of this invention, we provide pharmaceutical preparations containing a PAF-antagonist and a substance having an immune suppressant effect, generally containing up to 40% by weight of the immunosuppressive substance relative to the total amount of the active substance. Such

a preparation may be in association with a pharmaceutically acceptable carrier, diluent or excipient. A proportion of between 10 and 20% by weight is preferred. The amount of the PAF-antagonist in a preparation per single dose amounts to between 5 and 50 mg, when administered orally, and between 2 and 30 mg, when administered intravenously.

The effective compositions according to the invention may be used in the form of the conventional galenic preparations, for instance

1. Tablets

5 parts by weight of effective component according to the invention

1 part by weight of stearic acid

194 parts by weight of glucose

The components are compressed to form tablets of 200 mg.

2. Ampoule solutions

5 mg of effective component

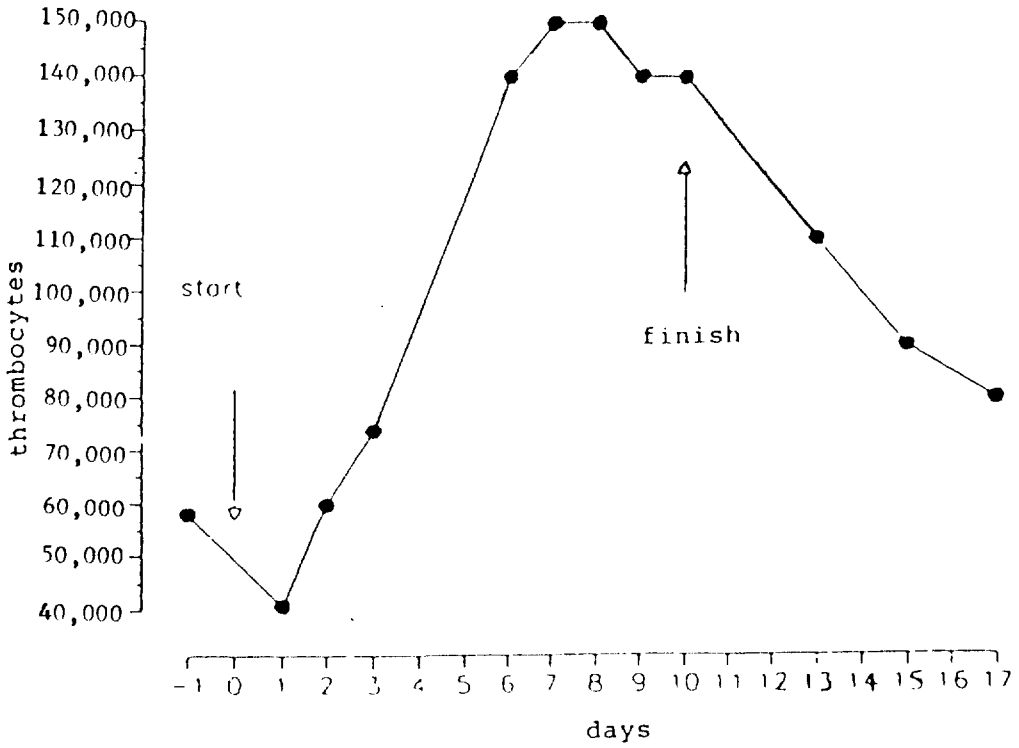
45 mg of sodium chloride

ad 5 ml Aqua pro inj

In Figure I, the number of thrombocytes is shown in thousands against the time in days. The treatment starts on day 0 and as expected, because of a certain latency, the number of thrombocytes drops again on the next day, to rise very rapidly to approximately normal levels of about 150,000 in the course of the treatment. After the treatment ends on the eleventh day, the number of thrombocytes also falls again, as expected.

The thrombocytes were counted by known methods using a Coultex Counter® Model S-Plus II.

Figure I



An important side-effect of cyclosporin in man is nephrotoxicity (Mihatsch MJ, Thiel G. Spichtin HP, Oberholzer M, Brunner FP, Harder F et al. Transplant Proc (1983) 15:2821-2835).

The treatment of male spontaneously hypertensive (SH) rats with cyclosporin causes damage to the kidneys which has been used as a model for cyclosporin nephrotoxicity (Reference:Ryttel B, Siegel H, Mueller AM, Hauser R, Mihatsch MJ, Transplant Proc (1985) 17:1430-1431).

This nephrotoxicity can be monitored by measurements of serum creatinine. Elevation of serum creatinine provides evidence of renal damage. Groups of 8 SH rats were dosed orally for 28 days either with 2, 25 or 50 mg/kg cyclosporin; 2, 25 or 50 mg/kg cyclosporin plus 13 mg/kg WEB 2170; 13 mg/kg WEB 2170 alone or vehicles (olive oil and water alone). Blood was removed before and 4, 13, 22 and 29 days after commencement of treatment. The mean level of serum creatinine in rats treated with cyclosporin plus WEB 2170 was lower than that for rats treated with cyclosporin alone. The effect was statistically significant ($0.05>p$). As an example, at 20 days mean creatinine levels in micromoles per litre serum were:

Vehicle	56
13 mg/kg WEB 2170 alone	55
2 mg/kg cyclosporin alone	59
25/mg/kg cyclosporin alone	93
50 mg/kg cyclosporin along	71
13 mg/kg WEB 2170 plus 2 mg/kg cyclosporin	53

13 mg/kg WEB 2170 plus 25 mg/kg cyclosporin	65
13 mg/kg WEB 2170 plus 50 mg/kg cyclosporin	67

Based on these results it appears that the combination cyclosporin/WEB 2170 may be associated with reduced nephrotoxicity in comparison with cyclosporin alone.

CLAIM:

1. A method of treating autoimmune diseases, including idiopathic thrombocytopenic purpura, in a human or animal subject which comprises administering to the said subject an effective amount of a PAF-antagonist selected from 4-(2-chlorophenyl)-9-methyl-2-[3-(4-morpholinyl)-3-propanon-1-yl]-6H-thieno[3,2-f][1,2,4]triazolo-[4,3-a][1,4]diazepine (Web 2086) and 6-(2-chlorophenyl)-8, 9-dihydro-1-methyl-8-[(4-morpholinyl)carbonyl]-4H, 7H-cyclopenta[4,5]-thieno-[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (Web 2170).

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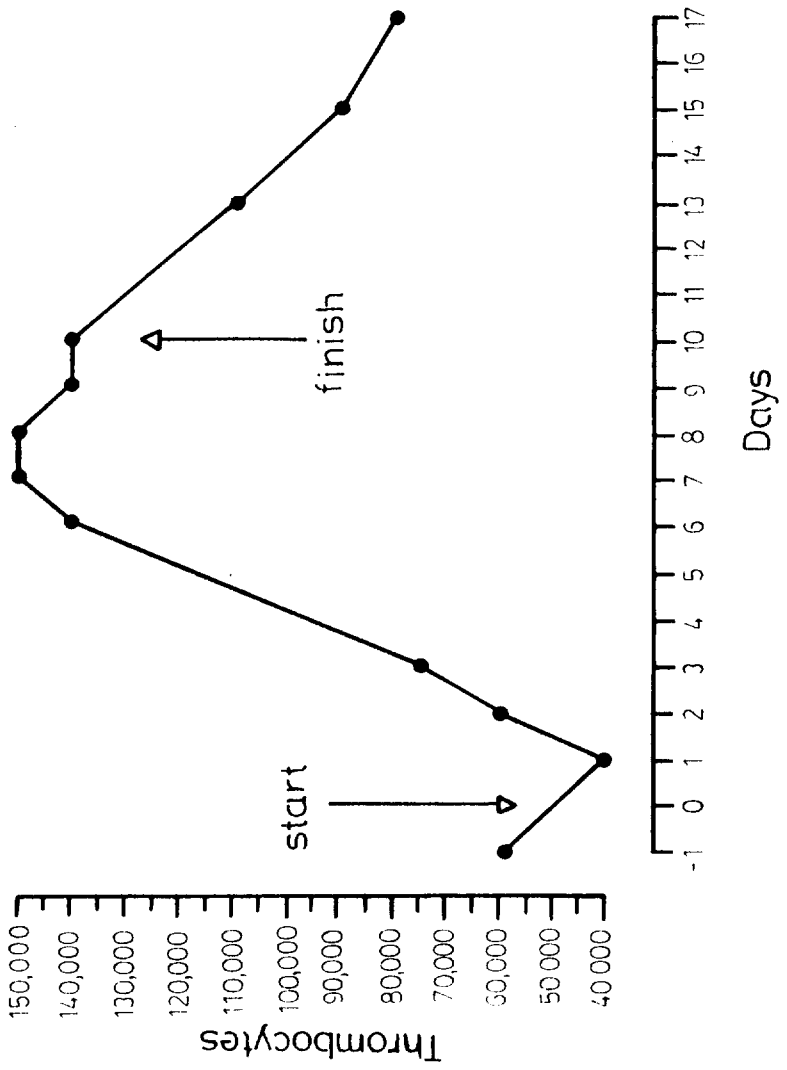
FIGURE 1



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