BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

D E C I S I O N
of 16 April 2002

Case Number: T 0251/97 - 3.3.4

Application Number: 88101669.5

Publication Number: 0278416

IPC: A61K 35/16

Language of the proceedings: EN

Title of invention:
Use of human blood coagulation factor XIII for the treatment of ulcerative colitis

Patentee:
HOECHST JAPAN LIMITED

Opponent:
Baxter Aktiengesellschaft

Headword:
Factor XIII/HOECHST JAPAN LIMITED

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Novelty (yes)"
"Inventive step (no)"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0251/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 16 April 2002

Appellant: (Proprietor of the patent)
HOECHST JAPAN LIMITED
10-16, 8-chome, Akasaka, Minato-ku
Tokyo (JP)

Representative:
Pfeil, Hugo, Dr.
Aventis Behring GmbH
Intellectual Property/Lega
P.O. Box 12 30
D-35002 Marburg (DE)

Respondent: (Opponent)
Baxter Aktiengesellschaft
Industriestrasse 67
A-1221 wien (AT)

Representative:
Polz, Leo, Dr.
Hoffmann, Eitle
Patent- und Rechtsanwälte
Postfach 81 04 20
D-81904 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 24 January 1997 revoking European patent No. 0 278 416 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
S. C. Perryman

Summary of Facts and Submissions

I. The appeal is against the decision of the opposition division revoking European patent No. 0 278 416 (application No. 88 101 669.5), which had been opposed by the respondent (opponent) on the grounds of lack of novelty and inventive step. The sole claim as granted read as follows:

"1. Use of human blood coagulation factor XIII for the production of a pharmaceutical composition to treat ulcerative colitis".

II. The following documents are cited in the present decision:

(D1) US-A-3 931 399;

(D2) Karatsuji T. et al., Haemostasis, Vol. 11, No. 4, pages 229-234 (1982);

(D3) Galloway M. J. et al., Clin. lab. Haemat., Vol. 5, pages 427-428 (1983);

(D4) Nilsson I. M. et al., Ann. Surg., Vol. 182, No. 6, pages 677-682 (1975).

III. Oral proceedings were held on 16 April 2002.

IV. The submissions by the appellant can be summarized as follows:

Novelty

- Ulcerative colitis (UC) was a disease etiologically different from pseudomembraneous colitis (PMC). UC was believed to follow from an inflammatory autoimmune process involving granulocytes. Inflammation ulcerated the mucosa and provoked bleeding. It was treated with anti-inflammatory agents (steroids) or immunosuppressive drugs. PMC was essentially due to endotoxins produced by continued growth of antibiotic-resistant bacteria such as Clostridium difficile during antibiotic treatment. These toxins caused necrosis of the mucosa (yellowish plaques of fibrin and necrotic material) and bleeding. Stopping antibiotic administration was usually the best therapy. Microbicides and antitoxin sera were also effective.

Inventive step

- The closest prior art was represented by document (D3), whose authors investigated the low level of factor XIII in the blood of patients suffering from UC. The biochemical aspect of this study dominated any clinical aspect to the extent that the document was silent as to the possibility of treating UC with factor XIII. In the introductory part of this document, reference was made to document (D2), according to which one patient suffering from PMC and having low levels of factor XIII, appeared to benefit from factor XIII infusions. The skilled person would not have combined the teachings of documents (D3) and (D2) and arrived at the claimed further medical use, for the reasons explained in detail hereinafter.

- Although both PMC and UC have inter alia mucosa bleeding as common symptom, the etiology of UC was different from that of PMC and was not fully understood before the priority date of the patent in suit (see under novelty). The authors of document (D3) in fact concluded that "the finding of reduced factor XIII subunit A and S levels in patients with chronic inflammatory bowel disease is a complex matter involving in vivo thrombin generation and non-specific protease activity.". In view of these differences and uncertainties as to the etiology mechanisms underlying PMC and UC, the fact that the infusion of factor XIII might have benefited **one single** patient (document (D2)) did not allow an extrapolation to be made to any kind of colitis. This was also the reason why the authors of document (D2) remained cautious by using expressions such as "appeared to benefit".

- According to document (D2) (see page 233, l-h column), a plasma level of factor XIII of 60% was sufficient to stop the intestinal bleeding. However, in the study according to document (D3) the patients already had blood levels of factor XIII exceeding this threshold (see Table 1). Hence no need would have arisen to treat them with infusions of factor XIII.

- According to document (D3), six patients were selected out of a total of thirteen suffering from chronic inflammatory bowel disease. No reasons were given why (page 427, l-h column) seven patients were excluded. Therefore, document (D3) did not demonstrate that there was a direct relationship between factor XIII deficiency and

UC.

- Merely restoring in UC the haemostatic function of factor XIII, ie only one of the many other clinically relevant signs and symptoms of UC, might not have been a sufficient measure to heal UC.

- Factor XIII infusion was considered by the authors of document (D2) as an "ultima ratio" because oral vancomycin was not available in Japan (see page 232, end of r-h column).

V. The submissions by the respondent can be summarized as follows:

Novelty

- Lack of novelty was no longer invoked as a ground for the patent in suit to be revoked (see paragraph XI of the decision under appeal).

Article 56 EPC

- The claimed second medical use relating to UC treatment with factor XIII would have been obvious even in the light of document (D3) alone, since in the introductory part of this document, reference was made to document (D2). The investigation carried out according to document (D3) had been made in response to the finding disclosed in document (D2) that UC could be successfully treated with factor XIII. The skilled person would have concluded that the treatment of PMC with factor XIII could be extended to UC, the more so

as document (D2) emphasised that any intestinal bleeding diseases would benefit from factor XIII treatment (see page 233, end of l-h column).

- Even if six of thirteen patients have been selected, there was no doubt that document (D3) established a direct relationship between UC and factor XIII depletion.

- It could be derived from document (D1) that factor XIII was a molecule capable of healing bleeding situations.

VI. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

Novelty

1. During oral proceedings before the opposition division, the opponent no longer invoked lack of novelty as a ground for revocation of the patent in suit. In the decision under appeal the opposition division concluded that UC was a disease etiologically different from PMC. The board agrees as well, so that the novelty issue need not be pursued further.

Inventive step

2. The parties consider document (D3) as closest prior

art. In the board's view, however, the main purpose of the work done according this document is to elucidate the mechanism responsible for the low level of factor XIII in five patients suffering from UC and in one patient affected by Crohn's disease (another form of colitis), both diseases being characterised by frequent episodes of bloody diarrhea. This investigation, based on determining the blood levels of subunits A and S of factor XIII and fibrinopeptide A (FPA) (see Table 1) pertains to analytical biochemistry rather than to therapy. In fact, the possibility of treating UC with factor XIII is not hinted at. As a secondary consequence, the document establishes via **diagnosis** that there is a direct relationship between factor XIII deficiency and the acute phase of UC and Crohn's disease (see page 427, l-h column, second paragraph).

3. In the introduction of document (D3), reference is made to document (D2), according to which one patient suffering from PMC and having low levels of factor XIII in blood, benefited from factor XIII infusions. In the board's view, it is the latter document which deserves more attention and hence represents the closest prior art. This is because it is concerned with clinical investigations on the **treatment** with factor XIII of PMC, a colitis which like UC is also characterised by intestinal bleeding as main symptom.

4. In the light of document (D2), the problem underlying the patent in suit is to find a further medical use of factor XIII. The problem is solved by the further medical use of factor XIII stated in claim 1, namely in the treatment of UC.

5. The skilled person faced with solving the above problem

would be aware that:

(i) Factor XIII is a coagulation factor which is converted to activated factor XIII (factor XIIIa) by thrombin and Ca^{++}. It acts as a transglutaminase which forms intermolecular amide bonds between monomers of fibrin and yields strong cross-linked nets which are thought to play a role in stopping bleeding and promoting wound healing (see document (D2), under "Introduction"). There is indeed an history of factor XIII used both against bleeding in general (see document (D1), column 4, line 13) and against bleeding in the gastro-intestinal sphere in particular, in cases where the blood level of factor XIII is low. In fact, document (D4) (see eg last paragraph on page 682) deals with the treatment of (factor XIII-deficient) acute erosive gastroduodenitis with factor XIII.

(ii) Treatment with factor XIII is successful in the case of UC (see document (D2)). The authors of this document are confident that factor XIII treatment can be extended to any other intestinal bleeding disorder characterized by low levels of factor XIII (see eg page 232, r-h column: "In any case, the present results suggest the importance of the haemostatic function in intestinal bleeding" and page 233, last sentence: "as well as in other intestinal bleeding disorders").

(iii) There is a direct relationship between factor XIII deficiency and the acute phase of UC (see

paragraph 2 supra).

On the basis of this knowledge, the skilled person would be highly confident that administration of factor XIII would be similarly effective in the treatment of UC in its active phase. In the present situation, the skilled person is provided with a clear hint from the prior art pointing in the direction of the claimed further medical use of factor XIII, and it is only necessary to confirm experimentally that the highly probable result is in fact obtained. The necessity of experimentally confirming a very much expected result does not render such obviously desirable confirmation inventive.

6. In view of the foregoing, the board finds that the use of factor XIII according to the sole claim at issue does not involve an inventive step, and so does not satisfy the requirements of Article 56 EPC.

7. The appellant argues that merely restoring in UC the haemostatic function of factor XIII, ie only one of the many other clinically relevant signs and symptoms of UC, might not be a sufficient measure to heal UC, especially if one takes into account the difference and uncertainties as to the etiology mechanisms underlying PMC and UC.

The board agrees that when the biochemical pathways leading to different pathological states are not fully understood, an oversimplified approach to possible treatments has to be avoided. However, in the present case, while it is true that the clinically relevant signs and symptoms of UC may be different from that of PMC, there is no doubt that the **principal** clinical

symptom of these diseases, to be kept under control, is bleeding. This is true not only in PMC/UC but also in other gastrointestinal diseases (see paragraph 5(i) supra). In summary, the scientific community considered that bleeding arrest was almost equivalent to healing and viewed the other clinical signs and symptoms of PMC or other intestinal bleeding disorders as less critical. This view is supported by the fact that in the patent in suit, much emphasis is also placed on bleeding as the principal symptom to be brought back to normality (see eg column 2, line 48; column 3, line 46 and column 4, lines 26-27: "bleeding had stopped").

8. The fact that document (D2) relates to the treatment of a **single** patient or that the authors use cautious expressions such as "appeared to benefit", in the board's opinion, does not mean that the skilled person had doubts as to whether the clinical data were correctly interpreted and whether the patient improvement was actually the result of infusions with factor XIII, since the finding arrived at in document (D2) was reliable to the extent that it prompted the further investigation carried out in document (D3).

9. Contrary to the appellant's view, the board also sees no flaw in the way the six patients have been selected out of the thirteen patients for further investigation according to document (D3). According to page 427, l-h column, second paragraph of this document, only those six patients having low levels of factor XIII at presentation took part in the further study and were successively diagnosed as having UC or Crohn's disease. Thus, apparently, the seven excluded patients had normal levels of factor XIII and suffered from a "chronic inflammatory bowel disease" other than UC and

Crohn's. This view is supported by the passage bridging the l-h and r-h column on page 428 ("all [the six] patients had an extensive colitis. These abnormal parameters [low factor XIII level] were not found when remission was obtained"). Therefore, it cannot be disputed that document (D3) establishes a direct link between UC and factor XIII depletion, at least in its acute phase.

10. The appellant argues that no need would have arisen to treat the patients referred to in document (D3) with infusions of factor XIII, since they already had blood levels of factor XIII exceeding the threshold (60%), which according to document (D2) was sufficient for stopping intestinal bleeding.

However, the value "60% or more" (see document (D2), page 231, l-h column, line 26), like the value "30%" (ibidem, line 23) relates to the plasma level of factor XIII as determined by the modified fluorescence method (see page 231, r-h column, line 16 from the bottom and Table I, "Hospital day" 14 in conjunction with "F-XIII, % (FM)", wherein "FM" means fluorescence method). The blood levels listed in Table 1 of document (D3), however, relate to factor XIII subunit A and subunit S. The comparison made by the appellant is thus not meaningful. Since document (D3) only deals with blood levels of factor XIII subunits, whilst document (D2) is concerned with blood levels of factor XIII and factor XIII subunit A, the only meaningful comparison could be that between the factor XIII subunit A threshold for healing UC reported in Table I of document (D2), namely 68% (see page 231, r-h column, lines 14-15 from the bottom and Table I, "Hospital day" 26 in conjunction with "F-XIII, % (LM)", wherein "LM" means Laurell's

method) and the blood levels of factor XIII subunit A listed Table 1 of document (D3). But the latter values (48%, 49%, 45%, 58%, 50% and 25%) turn out to be all below the 68% threshold. A need for treating the patients referred to in document (D3) with infusions of factor XIII would thus still arise.

11. Finally, the appellant maintains that factor XIII infusion was considered by the authors of document (D2) as an "ultima ratio" because oral vancomycin was not available in Japan (see page 232, bottom of the r-h column).

The lack of vancomycin in Japan may have forced the authors of document (D2) to turn to factor XIII as an "ultima ratio". But whatever the reason, they did make available to the public the technical teaching that it is worth treating PMC with factor XIII (see paragraph 5 (ii) supra). In any case, the board is not able to derive from the passage pointed out by the appellant on page 232, bottom of the r-h column of the document that vancomycin, if available, has to be preferred to factor XIII in the treatment of PMC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey