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D E C I S I O N
of 21 October 2004

Case Number: T 0986/02 - 3.3.4

Application Number: 92107685.7

Publication Number: 0512528

IPC: A61K 38/00

Language of the proceedings: EN

Title of invention:

Pharmaceutical compositions comprising an anticytokine

Patentee:

YEDA RESEARCH AND DEVELOPMENT COMPANY, LTD.

Opponent:

-

Headword:

Anticytokine/YEDA

Relevant legal provisions:

EPC Art. 56

Keyword:

"Inventive step - (yes)"

Decisions cited:

T 0606/89, T 0298/93, T 0800/99

Catchword:

-



Case Number: T 0986/02 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 21 October 2004

Appellant: YEDA RESEARCH AND DEVELOPMENT COMPANY, LTD.
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 19 July 2002
revoking European patent No. 0512528 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: S. C. Perryman
Members: M. Wieser
R. E. Gramaglia

Summary of Facts and Submissions

I. The appeal was lodged by the Patent Proprietors (Appellants) against the decision of the Opposition Division, whereby European patent No. 0 512 528 was revoked under Article 102(1) EPC. It had been opposed by one party under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and Article 100(b) EPC for lack of sufficiency of disclosure (Article 83 EPC).

II. Claim 1 of the patent as granted read:

"Use of a Tumor Necrosis Factor Binding Protein (TBP), a salt, a functional derivative, a precursor or an active fraction thereof, or combinations of the foregoing, for the manufacture of a pharmaceutical composition for the treatment of systemic lupus erythematosus."

Dependent claims 2 to 6 referred to preferred embodiments, wherein the TBP was further characterised. Claim 7 related to a process for the manufacture of a pharmaceutical composition for the treatment of systemic lupus erythematosus (SLE) using a TBP as defined in any of claims 2 to 6.

III. The Opposition Division, while deciding the issues of priority, sufficiency of disclosure and novelty in favour of the Appellants, decided that the subject matter of the claims as granted did not involve an inventive step in the light of the following documents:

(1) EP-A-0 398 327

(4) EP-A-0 308 378

(10) Nihon Univ. J. Med., vol. 32, 1990, p. 297 to 301

(16) Arthr. Rheum., vol. 32, 1989, no. 2, p. 146 to 149

Moreover, the Opposition Division decided that the subject-matter of the claims did not involve an inventive step as the technical problem underlying the invention had not been solved.

IV. The Opponents withdrew their opposition on 19 July 2002 and ceased to be a party in respect of substantive issues.

V. The Board expressed their preliminary opinion in a communication dated 29 March 2004. Oral proceedings were held on 21 October 2004.

VI. The Appellants requested that the decision under appeal be set aside and that the patent be maintained as granted or on the basis of claims 1 to 6 of the auxiliary request filed on 20 August 2004.

VII. Besides those mentioned in section (III) above, the following documents are referred to in this decision:

(5) Physiological and Pathological Effects of Cytokines, 1990 Wiley-Liss Inc., p. 111 to 116

(6) J. Immunol., vol.141, no. 9, 1988, p. 3050 to 3054

- (7) Clin. Invest. Med., vol. 12, no. 4, 1989, B96,
Abstract R-586
- (7a) Clin. Invest. Med., vol.12, no.4, 1989, B96,
Abstract R-582
- (9) Kidney Int., vol. 37, no. 1, 1990, 411
- (17) Clin. exp. Immunol., vol. 85, 1991, p. 386 to 391
- (18) Nature, vol. 331, 1988, p. 355 to 357
- (19) Clin. Immunol. Immunopath., vol. 52, 1989, p. 421
to 434
- (22a) and (22b)
Graphic presentation of the data of table 1 of the
patent in suit; submitted by the Appellants on
29 November 2002
- (23) Acta Med. Hung., vol. 46, no. 4, 1989, p. 245
to 252 (abstract)
- (24) Arthr. Rheum., vol. 44, no. 7, 2001, p. 1721
to 1722

VIII. The submissions by the Appellants as far as they are relevant to the present decision may be summarised as follows:

Before the relevant date of the patent in suit the method of choice for treatment of SLE was the administration of corticosteroids, like prednisone, which work in a non-specific, non-mechanism related way

by reducing the immune-stimulation of a patient. These substances, especially when administered in a long term therapy, had severe side effects and could be the reason of permanent organ damage.

Contrary to this the invention pinpointed the mechanism of the disease by realizing the correlation between elevated TNF levels and increasing disease activity.

Nothing in the prior art would have encouraged the skilled person, trying to find an alternative way for treatment of SLE, to consider the administration of TBPs. There was no clear indication that human SLE patients showed an elevated level of TNF. The isolated publications which did mention elevated TNF levels in sera of SLE patients, found these only under specific circumstances, such as chronic infections (document(16)), or contained no data at all and were contradictory in themselves (document (10)). No conclusion could be drawn that elevated TNF levels might be responsible for increasing disease activity. Inconsistent data in mice showed a protective effect of TNF in some strains affected with SLE.

The technical problem underlying the invention, namely the provision of an alternative treatment for SLE, has been solved by the patent. The interpretation of the experimental data of examples 1 and 2 allowed the unambiguous conclusion that TBP was suitable for therapy of SLE, which was confirmed by post published documents.

Reasons for the Decision

Main Request

1. The Board sees no reason to differ from the decision under appeal on the issues of priority (Articles 87 to 89 EPC), sufficiency of disclosure (Article 83 EPC) and novelty (Article 54 EPC), decided in favour of the Appellants.
2. When assessing inventive step, the Opposition Division considered document (1), or likewise document (4), as representing the closest state of the art.

Document (1), originating from the Appellants, discloses that the level of TBP-II in sera of patients can be used as a marker for SLE (page 6, lines 43 to 51 and example 8). Furthermore, on page 7, lines 22 to 24 it is said that TBP-II can be used for the treatment of "...any condition where there is an overproduction of endogenous TNF, such as in cases of septic shock, cachexia, graft-versus-host reactions, autoimmune diseases like rheumatoid arthritis etc." An identical statement can be found on page 11, lines 47 to 49 of document (4), also from the Appellants.

3. Starting from this prior art, the Opposition Division defined the technical problem to be solved as the provision of a further therapeutical use of TBP. The skilled person, in the light of the disclosure in document (10) or document (16), would consider SLE treatment to be such further therapeutic use.

4. For objectively assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal consistently apply the "problem and solution approach", which requires as a first step the identification of the closest prior art. In accordance with the established case law of the boards of appeal (cf decisions T 800/99 of 17 January 2001 and T 606/89 of 18 September 1990) the closest prior art is generally a document conceived for solving the same problem or aiming at the same objective and which requires the minimum of structural and functional modifications. Ideally, that purpose should be something already mentioned in this prior art document as a goal worth achieving (cf decision T 298/93 of 19 December 1996, point 2.2.2).

5. The Board takes the view that the invention underlying the patent in suit serves the purpose to provide a treatment for SLE. In the light of the criteria for identifying the closest prior art as elaborated by the Boards of Appeal, a document aiming at the same purpose, i.e. treatment of SLE, is considered to be the most appropriate starting point for the objective assessment of an inventive step following the criteria of the "problem and solution approach".

6. Document (7a), an abstract published on the same page of a scientific magazine as document (7), describes the treatment of SLE patients with corticosteroids, and in detail refers to the effects of prednisone administration on neuropsychological functioning in SLE. As acknowledged by the Appellants, administration of corticosteroids, which work in a non-specific, non-SLE-mechanism related way by reducing the immune-

stimulation of a patient, is used in the art to suppress disease symptoms attending SLE.

The Board considers document (7a) to be directed to the same purpose or effect as the invention, and thus to be treated as being the closest prior art for assessing inventive step (Article 56 EPC). Starting from this closest prior art, the Board considers that the objective technical problem underlying the present invention must be seen in the provision of an alternative treatment of SLE.

The question to be answered is, whether or not the cited prior art documents contain information that would encourage a skilled person, trying to solve this problem, to modify the disclosure in the closest prior art and to arrive at the claimed subject-matter in an obvious way.

7. Document (7a) itself does not contain a hint pointing at the administration of substances other than corticosteroids for the treatment of SLE.

Document (1), while explicitly referring to TBP-II as diagnostic marker for SLE, in the passage disclosing possible therapeutic applications of TBP-II does not mention SLE (see point (2) above). The same applies to document (4).

8. Document (10) reports that the level of TNF mRNA was found to be increased in three patients with SLE (abstract and page 299, first full paragraph). On page 300, first paragraph it is stated that monocytes from SLE patients, on stimulation with silica particles

produced **lower** amounts of TNF- α than did normal monocytes. A few lines below it is said that significantly **elevated** levels of TNF- α have been observed in sera of patients with SLE when compared with levels in healthy controls. Reference is made to a document (19), which is an article from the authors of document (10) with the title: "Impaired tumor necrosis factor production and abnormal B cell response to tumor necrosis factor in patients with systemic lupus erythematosus". According to the list of references on page 301 of document (10) this document was "submitted for publication".

This document has been published after the priority date of the patent in suit and has been cited as document (17) in the present procedure. In the abstract and on page 390, lines 3 to 33 thereof it is reported that a **decreased** TNF mRNA expression was observed in peripheral blood mononuclear cells from patients with SLE stimulated by mitogens.

Thus, the statement on page 300 of document (10) referring to elevated levels of TNF- α in sera of SLE patients, which is not supported by any experimental data, stands in contradiction to another statement in the same document a few lines above and also to the findings of the same authors in a later publication.

Accordingly, the disclosure in document (10), concerning TNF levels in sera of SLE patients is not suited to provide the skilled reader with a clear teaching but rather creates a confusing situation. Even if the skilled person would learn from this document that elevated TNF levels might be possible, he would

not get a hint to use this knowledge for a new approach to treat the disease.

9. Document (16) discloses the results of the determination of serum TNF levels in 22 SLE patients. It is said that SLE patients have either normal or slightly elevated TNF levels, while all SLE patients with concomitant infections had elevated, markedly raised levels (abstract). On page 147, end of right column, it is said that the median TNF level in the SLE patients without infection was within the normal reference range. No significant correlation was found between the levels of TNF and anti-ds DNA antibodies in SLE patients (page 148, left column), which are accepted as being a reliable and sensitive indicator of the SLE disease activity.

Elevated TNF serum levels are known to be a response to infection. It can be concluded from the teaching in document (16) that this TNF response to infections is similar in SLE patients and other, healthy subjects. Document (16) does not mention that TNF levels correlate with SLE disease activity and does not point to a method for treatment of the disease.

10. Document (23) discloses that monocytes from SLE patients have been found to produce significantly less TNF- α than those of healthy controls. A skilled reader would therefore not consider TNF to play a role in SLE development and disease activity.

11. Several of the cited prior art documents deal with data obtained from a mouse model of the disease. Documents (18) and (19), which make use of the NZBxNZW F₁ hybrid mouse, report that TNF- α administration improved the survival rate relative to control mice and delayed the progression of the disease and the development of nephritis. Thus, TNF administration seems to protect this mouse strain from SLE. This points in exactly the opposite direction as does the patent in suit, namely buffering excess levels of TNF by administration of TBP.

Document (5), using a different mouse strain, discloses that mice with SLE exhibited elevated levels of spontaneous or induced IL-1 and TNF (page 114). The document then goes on to say: "Of particular interest are the high levels of IL-1 secreted by the stimulated macrophages of the sick mice." The skilled person, learning that besides TNF other cytokines, like IL-1, are involved in experimental SLE, does not get a hint to focus on TNF.

Documents (6), (7) and (9), observing MRL/lpr mice, disclose that animals of this strain with lupus nephritis show increased levels of a number of cytokines (IL-1 β and TNF in document (6), IFN- γ and TNF- α in documents (7) and (9)). None of the documents hints at a SLE treatment based on buffering elevated TNF levels.

12. Thus, the data obtained by various research groups observing different strains of mice suffering from SLE or lupus nephritis, are not consistent and do not

contain information leading the skilled person to focus on TNF for a possible treatment of the disease.

The data obtained in different mouse models are commented on in post-published document (24), which supposes on page 1721, right column that TNF- α may have a dual role in SLE mice, as it seems to be protective in some strains (like NZBxNZW) while it may exacerbate the disease in other strains.

13. To summarize, the data obtained in mouse models are inconsistent. The cited prior art documents contain contradictory statements with regard to the question whether the TNF level in serum from human SLE patients, when compared with healthy controls, is reduced, normal or elevated. None of the documents discloses a conclusion or contains a suggestion that would encourage the skilled person, in order to solve the problem underlying the present invention, namely to provide an alternative treatment for SLE, to focus on TNF and to modify the closest prior art in an obvious way to arrive at the subject-matter of claims 1 to 7.

14. The Opposition Division, on page 5 of the decision under appeal, found that the claims do not comply with the requirements of Article 56 EPC, as it has not been shown that the technical problem has been solved. The Opposition Division criticizes that no in vivo results showing the beneficial effect of TBP administration are provided, and that additional prednisone administration to the patients does not allow an unambiguous interpretation of the data.

15. The results of example 1 are shown in table 1 of the patent and have been graphically presented in documents (22a) and (22b). These graphs show that the endogenous TBP levels reach a plateau when the disease proceeds. As a consequence the TNF shedding capacity, which is considered to be a natural safeguard against the detrimental effects of this cytokine, arrives at its maximum and additionally formed TNF cannot be buffered. At the same time, as shown in table 1 of the patent in suit and in documents (22a) and (22b), the disease index and the level of anti-ds DNA antibodies, a reliable and sensitive indicator of the SLE disease, further increase. It is concluded that the clinical deterioration of the patients under observation has to be attributed to further increasing amounts of bio available, free TNF. To attenuate the progression of the disease, administration of exogenous TBP is suggested to neutralise excess TNF. Example 2 shows, in an in vitro set up, that the cytotoxic activity of TNF can effectively be neutralized by administration of TBP.

The Board is convinced that the interpretation of these experimental data allows the conclusion that TBP is suitable for therapy of SLE.

16. At the priority date of the patent in suit no TBP for human use was available so that in vivo human tests could not be carried out. As the mouse model for SLE is not representative for human SLE (see points (12) to (13) above), no additional data, besides those provided by examples 1 and 2, could have been presented by the Appellants.

17. Different from prednisone, which is administered to reduce the immune-stimulation of a patient, TBP is not intended merely to suppress symptoms of SLE, but to combat the primary cause of the disease. Since prednisone dosage is not the cause of the disease symptoms (like formation of anti-ds DNA antibodies), but is intended merely as a palliative, the Board does not see that prednisone administration invalidates the interpretation of the data obtained in example 1 as showing the beneficial effect of administering TBP.

18. Consequently, the Board, finding that the subject-matter of claims 1 to 7 of the main request is not obvious in the light of the cited prior art documents, and that the problem underlying the patent in suit is solved by the claimed subject-matter, decides that the requirements of Article 56 EPC are met.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar:

The Chairman:

P. Cremona

S. C. Perryman