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Datasheet for the decision of 18 June 2015

Case Number: T 1243/12 - 3.3.04

Application Number: 00928991.9

Publication Number: 1176981

IPC: A61K39/395

Language of the proceedings: EN

Title of invention:
Treatment of autoimmune diseases with antagonists which bind to B-cell surface markers

Patent Proprietor:
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Biogen Inc.

Opponents:
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02: MEDIMMUNE, INC.
03: Elend, Almut Susanne
04: CENTOCOR, INC.
05: GLAXO GROUP LIMITED
06: Merck Serono SA
07: Genmab A/S
08: Wyeth LLC

Headword:
Treatment of autoimmune diseases/GENENTECH

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

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Case Number: T 1243/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 18 June 2015

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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted on 13 April 2012 revoking European patent No. 1176981 pursuant to Article 101(3)(b) EPC.

Composition of the Board:

Chairman B. Claes
Members: A. Chakravarty
M.-B. Tardo-Dino

Summary of Facts and Submissions

I. An appeal was lodged by the patent proprietors (appellants) against the decision of the opposition division revoking European patent No. 1 176 981 entitled "*Treatment of autoimmune diseases with antagonists which bind to B cell surface markers*". The corresponding patent application was published as international application WO 00/67796.

II. The patent was opposed by eight parties (opponents 01 to 08, now respondents I to VIII) under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Articles 100(b) and 100(c) EPC.

III. Opponent 01 also lodged an appeal but withdrew it at the beginning of the oral proceedings before the board.

IV. The proceedings before the opposition division constituted the further opposition proceedings, following remittal of the case by the present board in a different composition, in appeal case T 495/09 of 1 June 2010, in which it was decided that claim 1 of the auxiliary request filed on 30 April 2010, met the requirements of Article 123(2) EPC.

V. The opposition division based its decision revoking the patent on a main request (identical to the auxiliary request considered by the board in decision T 495/09, *supra*) and an auxiliary request, both filed with a letter dated 6 March 2012 and each consisting of a single claim.

VI. With the statement of grounds of appeal, the appellants requested that the decision of the opposition division

be set aside and that the patent be maintained on the basis of the main request or alternatively on the basis of the auxiliary request. The claim of the main request read:

"1. Use of rituximab in the manufacture of a medicament for treatment of rheumatoid arthritis in a mammal, wherein the medicament is for administration with methotrexate to the mammal".

VII. The parties were summoned to oral proceedings and the board issued a communication in which some of the issues to be discussed during the oral proceedings were set out.

VIII. Respondents II to IV and VII, informed the board that they would neither attend nor be represented at the oral proceedings. Respondent III also requested that the appeal be dismissed.

IX. Oral proceedings before the board were held on 18 June 2015 in the absence of the respondents II to IV and VII. During the oral proceedings, the appellants withdrew the auxiliary request. The final requests of the appellants were that the decision under appeal be set aside and the patent be maintained on the basis of the main request. Respondents I, III, V, VI and VIII requested that the appeal be dismissed. At the end of the oral proceedings the chairman announced the board's decision.

X. The following documents are referred to in this decision:

D8 : Edwards J. and Cambridge G., British J. Rheumatol., 1998, 37, 126 - 130.

D15: Edwards J., New England J. Med., 2004, 350(25), 2572 - 2581.

D25: Edwards J. and Cambridge G., Rheumatology, 2001, 40, 205 - 211.

D56: Declaration by Jonathan Edwards dated 27 February 2008, including Appendices A to I, Appendix H consisting of Patient Records

D81: Kremer J., Arthritis Rheum., September 1998, 41(9), 1548-1551.

D82: Maini R. et al., Arthritis Rheum., September 1998, 41(9), 1552-1563.

XI. The arguments of the appellants can be summarised as follows:

Document D56 was considered to represent the closest prior art for the claimed invention. It concerned the treatment of rheumatoid arthritis (RA) with rituximab (RTX) which was based on RTX's unique mechanism of action. Document D81, on the other hand, primarily concerned the long-standing treatment of RA with methotrexate (MTX) and did not even mention RTX or biological interventions using its mechanism of action. Furthermore, document D56 represented a study carried out on patients that had repeatedly failed to respond to other conventional treatments, while document D81 was completely speculative.

Document D15 (Fig. 2) demonstrated that the combination of MTX and RTX was better than RTX alone or RTX with cyclophosphamide in the treatment of RA. Thus, when starting from document D81 as closest prior art the

problem to be solved was the provision of an improved treatment of RA. The claimed solution involved an inventive step because there was no suggestion in the prior art that administration of RTX with MTX would lead to such improved treatment.

Furthermore, even not taking the evidence of post-published document D15 into account in assessing inventive step of the claimed subject-matter, the skilled person starting from document D81 would not have combined methotrexate (MTX) with rituximab (RTX) as a therapy for rheumatoid arthritis (RA) because there was no incentive in the art to do so, but rather a direct disincentive. It had to be borne in mind that document D81 had be triggered by the publication in the same journal issue of document D82, which concerned the combination of an anti-TNFα monoclonal antibody with MTX for the treatment of RA. In contrast to the invention, this combination aimed at inhibiting the production of human anti-chimeric antibodies (HACA) against the anti-TNFα antibodies, which however would not have been as concern for the skilled person considering treatment of RA with RTX because nothing in the art that suggested that HACA was a problem for patients receiving RTX. Indeed RTX functioned by depleting B-cells, which was not the case for the other types of biologic agents addressed in document D81.

A second reason why the skilled person would not have combined MTX with RTX for the treatment of RA was the state of the art would not have given the skilled person any cause to expect a synergy, in the sense of mechanistic complementarity, between the two agents in treating RA. MTX could not contribute to achieving the goal of total depletion of B-cells which was aimed at by RTX treatment.

Finally, the skilled person would have been positively discouraged from combining MTX with RTX to treat RA in patients because document D81 disclosed that the combination of MTX with biological drugs was not completely understood and was associated with certain "*perils*".

XII. The arguments of the respondents can be summarised as follows:

Document D81, which represented the closest prior art for the purposes of assessing inventive step of the claimed use, was a general review of what was known in 1998 about combination therapy with biologic agents in RA. In particular, it disclosed that MTX was accepted as the "*most efficacious and best-tolerated single agent for the treatment of rheumatoid arthritis*" (introduction, page 1548, left column). It further suggested that both existing and newly developed drugs offered considerable potential for additional therapeutic benefit when used with MTX and that these should be empirically tested in combination with MTX without waiting for a complete determination of their mechanism (page 1550, left hand column, paragraph 1).

The public prior use represented by document D56 aimed to study the utility of RTX for treating RA and did not aim at combining a biologic agent with methotrexate to treat RA and was therefore a less suitable starting point for assessing inventive step than document D81.

The technical difference between the treatment disclosed in document D81 and the claimed subject-matter was that in the claimed treatment, the biological agent to be used with MTX was RTX. The skilled person was therefore faced with the technical problem of the provision of an

alternative biological agent to be used in combination with MTX in the therapy of RA or simply the provision of an alternative therapy for RA.

In view of the fact that both MTX and RTX were known as agents useful in the therapy of RA and also considering that document D81 discussed combination therapy of biological agents with MTX in RA therapy, there was a clear incentive for the skilled person to use MTX in combination therapy with any biological agent, including RTX.

In relation to the question of the alleged lack of a rationale for combining MTX with RTX in the absence a known problem of a human anti-chimeric antibody (HACA) response to RTX, it had to be remembered that document D82 disclosed RA therapy with MTX in combination with a monoclonal antibody not only to counter a HACA response but also because of MTX's known disease modifying properties.

Although document D81 mentioned certain perils and unanswered questions associated with therapy of RA by a combination of biological agents and MTX, a fair reading of the document showed that it advocated a "*try and see*" approach with respect to the biological agents to combine with MTX. The skilled person would therefore have combined any biologic agent with MTX.

Post-published document D15 should not be taken into account in the assessment of inventive step of the claimed subject-matter because the application as filed did not foreshadow this alleged synergistic effect. Furthermore, the document did not even disclose a surprising synergistic effect between RTX and MTX in the treatment of RA. In fact Figure 2 showed that patients

receiving rituximab and methotrexate seemed to be comparatively better than those treated with rituximab and cyclophosphamide only because the patients who had been given the latter combination had not received any treatment since day 17, whereas the patients on the former were still receiving a weekly dose of MTX.

Reasons for the Decision

1. The appeal of the patent proprietors is admissible.

2. During the oral proceedings before the board, the parties were heard on the requirements of Article 54 EPC of the subject-matter of claim 1 of the main request and the board expressed its opinion on this matter. However, in view of its conclusions on inventive step (Article 56 EPC) in respect of this subject-matter, there is no need to to provide detailed written reasons for this opinion.

Claim construction

3. The board considers that the skilled person would understand that the medicament to be prepared according to the claimed use (see Section VI.) may comprise rituximab (RTX) alone or may comprise both RTX and methotrexate (MTX) and that the claim is for uses involving the deliberate treatment of rheumatoid arthritis (RA) with both of RTX and MTX. Since the claim includes no indication of timing or sequence of the administration of either active component, the RTX containing medicament to be manufactured according to the claimed use may be administered with MTX separately or together, at the same time or at a different time. The RTX and MTX may be administered in either order.

Inventive step - Article 56 EPC

The closest prior art

4. There was a difference in opinion between the parties as to which document represented the closest prior art for the claimed invention. The appellants chose document D56, whereas the respondents selected document D81, as did the opposition division in the decision under appeal.

5. Document D81 is an editorial in a scientific journal concerning combination therapy of RA with MTX with certain biological agents, in particular, monoclonal antibodies. Document D56 is a declaration by Professor Jonathan Edwards, dated 27 February 2008, relating to a five patient open label clinical study aiming to investigate the treatment of RA with RTX. The document includes appendices A to H, where appendix H is a set of record sheets of patients participating in the study. The public availability of the study and the treatments used was not disputed by the appellants.

6. It has been established in the case law of the Boards of Appeal that, where more than one document is cited as the closest prior art, the one which must be deemed the closest is that which provides the skilled person with the most promising springboard to the invention (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition, 2013, I.D. 3.4.).

7. In the present case, in deciding which of documents D56 or D81 should represent the closest prior art for assessment of inventive step of the claimed subject-matter, the board recognises that both documents are good candidates. However, the board has satisfied itself

that the claimed subject-matter was not inventive when starting from the disclosure of document D81 (see point 18., below). This document may therefore be taken to represent the closest prior art.

Problem to be solved

8. The difference between the disclosure of document D81 and the claimed invention lies in the choice of RTX as the biological agent to be administered with MTX.

9. The appellants argued that treatment of RA with a combination of MTX and RTX provided an unexpected therapeutic synergy. The evidence for this therapeutic synergy was to be found in document D15. Accordingly, the problem to be solved was the provision of an **improved** treatment of RA.

10. In accordance with the case law of the boards, reformulation of the problem to take a technical effect into account is only allowable, if the new problem can be deduced from the application as filed. In the same vein, the case law of the boards has consistently held that post-published evidence to support that the claimed subject-matter solves the technical problem underlying the invention, is taken into account only if it is already credible from the disclosure in the patent that the problem is indeed solved (see Case Law of the Boards of Appeal of the European Patent Office, 7th Edition, 2013, I.D. 4.4.1, 4.4.2 and 4.6). In other words, a subsequently invoked technical effect cannot be taken into account when determining the problem underlying the invention if it could not be deduced by the skilled person from the application as filed (see Case Law of the Boards of Appeal of the European Patent Office, 7th Edition, 2013, I.D. 4.4.2).

11. The board notes that document D15 was published after the effective date of the patent in suit. Moreover, the board cannot identify in or deduce from the patent any disclosure of a synergistic effect between the two agents which would amount to a teaching to be backed up by the disclosure of document D15. The disclosure of document D15 is therefore not taken into account in the assessment of the inventive step of the claimed subject-matter.

12. Accordingly, starting from the disclosure in document D81, the technical problem to be solved is the provision of an **alternative** biological agent (drug) to be used in combination with methotrexate for the treatment of rheumatoid arthritis.

Obviousness

13. The question to be answered by the board is whether the skilled person starting from therapies for RA disclosed in document a document D81 and seeking a solution to the above formulated technical problem, would have considered administration of MTX with RTX for the treatment of RA.

14. Document D81 teaches that methotrexate (MTX) was accepted as "*the most efficacious and best-tolerated single agent for the treatment of rheumatoid arthritis (RA)*". The treatment of RA with the biological agent RTX was also known to the skilled person, at least from the public prior use represented by document D56. Neither of the above facts is a matter of dispute among the parties.

15. Document D81 discloses that RA patients would benefit from a lowering of the weekly dose of MTX administered

(see document D81, page 1548, column 2, penultimate paragraph). That such a lowering might be achieved through the combination of MTX with a new "biotechnology" agent is also disclosed. On the subject of "[*w*]*hich combination [of biologic agent and MTX] makes the most sense*" document D81 concludes that "[*b*]*ecause of these uncertainties about the mechanism of action of MTX and cytokine inhibition, neither TNFα or IL-1β inhibitors can claim to be inherently better positioned to promote their use with MTX as making the most conceptual sense. Therefore, these and* ***other*** *biotechnology interventions are, quite reasonably, being empirically combined with MTX while hoping for the best. This approach can, and should, be advocated because our patients simply do not have the time to wait until we determine how all of the new and existing drugs work, let alone how MTX works"* (page 1550, column 1, paragraph 1). Document D81 furthermore states: "*Nevertheless, the current practice of* ***combining virtually all new agents with MTX****, the drug of many therapeutic possibilities, makes it likely that the cart will come before the horse. That is,* ***we will empirically determine the combinations which result in the very best clinical efficacy*** *and then investigate the effects on the immune and inflammatory cascade. This has been the scenario which has occurred with MTX as monotherapy as the scientific community began to recognize its clinical value*" (page 1550, paragraph 2; emphasis added by the board).

16. In summary, the board concludes that document D81 suggested to the skilled person that the standard therapy of RA with MTX could be improved by administering it in combination with biological agents, in particular antibodies, newly developed for the treatment of RA. Given the urgency of the need for

improved treatments, rather than waiting for a complete understanding of the mechanism of action of such agents or indeed of a complete understanding of the mechanism of action of MTX, an empirical approach to combination therapy was advocated. Following this empirical approach, the skilled person would have considered treating RA in a patient by administering MTX in combination with any new biological agent developed to treat RA. Thus, given that RTX was one such newly developed biological agent, the board takes the view that the skilled person had an incentive to administer MTX in combination with RTX to treat RA.

17. The appellants submitted that the skilled person, starting from document D81 as closest prior art, would not have combined MTX with RTX as a therapy for RA because there was no scientific rationale for combining the two agents and also because the disclosure of document D81 provided a disincentive to the skilled person concerning such combinations (see section XI.). However, in view of the board's conclusion that document D81, contrary to the appellants' views, provided the skilled person an incentive to empirically combine any new biological agent developed for treating RA, with MTX for the treatment of RA, regardless of the mechanism of either agent, these arguments cannot succeed.

18. Thus, the board concludes that the subject-matter of claim 1 lacks an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

P. Cremona B. Claes

Decision electronically authenticated