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Demand Regarding Enbrel (Etanercept)

Purpose of the Demand

1. Wyeth KK should promptly complete the "long-term (at least one year) double-blind comparative clinical study with appropriate control groups to verify the efficacy, safety, and the like of Enbrel in preventing the progression of articular destruction during treatment with 10 mg and 25 mg," which was established as the second condition of approval on January 19, 2005 for Enbrel (generic name: "etanercept"). The completion of the study should be followed by a prompt review, and the results of the review should be publicly disclosed.

2. Until the efficacy and safety of the Enbrel 25 mg dosage form are confirmed by a review of the results of the study outlined in the above section 1 of this demand, the Ministry of Health, Labour, and Welfare (MHLW) should approve the 10 mg dosage form and should modify the method of administration so that the currently approved 25 mg dosage form would be used only in exceptional cases where the 10 mg dosage form is ineffective, and this change should be fully publicized.

3. The Japan College of Rheumatology (Antirheumatoid Post-Marketing Surveillance Special Committee) should again review the results of the all-patient surveillance conducted by Wyeth, and should publicly disclose the results.

Reason for the Demand

1. Introduction: Summary of Enbrel and Problems

(1) Summary of Enbrel

Enbrel ("etanercept", manufactured by Wyeth KK, distributed by Takeda Pharmaceutical Co., Ltd., referred to below as "Enbrel") is an anti-TNF-α inhibitor (binds to TNF-α present in most sites of rheumatoid arthritis, so as to prevent TNF-α from acting on articular cells and causing tissue destruction) which was approved, with the four following conditions of approval, as being indicated for "rheumatoid arthritis (limited to when existing therapy is ineffective)" on January 19, 2005. The Dosage and Administration for Enbrel in the package insert is "10 mg to 25 mg given once a day twice weekly by subcutaneous injection."

※ Four Conditions of Approval

1. For a certain period of time post-marketing, all treated cases should be registered to investigate the safety and efficacy of Enbrel, and the collected results should be regularly reported.
2. A long-term (at least one year) double-blind comparative clinical study with appropriate control groups should be conducted to verify the efficacy, safety, and the like in preventing the progression of articular destruction during the administration of 10 mg and 25 mg, the results should be promptly reported, and the appropriateness of the Dosage and Administration should be reviewed.
3. A large-scale post-marketing surveillance should be conducted, and the safety of Enbrel should be thoroughly reviewed, with a greater focus on the safety of long-term treatment and the development of infections and the like such as tuberculosis.
4. Appropriate measures for self-administration should be implemented so that it is done only in patients in whom efficacy is confirmed and the absence of safety problems can be determined.

(2) Problems

The committee contracted The Informed Prescriber (TIP) and the Non-Profit Organization Japan Institute of Pharmacovigilance (NPOJIP) to review the efficacy and safety of Enbrel.

According to the "Report on Review of Efficacy and Safety of Etanercept" prepared by the above contracted organizations, Enbrel was found to have major problems in terms of efficacy and safety. Problems related to the conditions of approval in Japan were also identified in the course of the review.

These problems included the following: ① there is no significant difference in the effects between the Enbrel 25 mg and 10 mg dosage forms, yet the adverse effects of the 25 mg dosage form appear to be significantly greater than those of the 10 mg dosage form; ② only the 25 mg dosage form has been approved and is being used pending the results of the comparative study on the 10 mg and 25 mg dosage forms called for in the conditions of approval; ③ the reliability of the all-patient surveillance, which was a condition of approval, is open to question; and ④ the process of deliberation was cursory. These problems have led to this demand. Each of these is addressed in greater detail below.

2. Problem ①: Efficacy and Adverse Effects of Enbrel 10 mg and 25 mg Dosage Forms

(1) Perspective: Benefit-to-Risk Ratio

A generally recognized principle of therapy is that the benefits of treatment must outweigh the risks in order to recognize the legitimacy of a certain therapy.

TNF-α is expressed more the greater the severity of rheumatoid arthritis, and the benefits obtained with the use of a TNF-α inhibitor may therefore be greater the more severe the disease. However, the potential for developing cancer or the chance of infection does not depend on severity, and a certain degree of harm will presumably result from the inhibition of TNF-α regardless of the severity of rheumatoid arthritis. Thus, in severe cases, the benefits of treatment may outweigh the risks, but as patient severity diminishes, the balance is reversed, and the risks of treatment may outweigh the benefits.

Only the 25 mg dosage form of Enbrel is currently approved in Japan, but does the 25 mg dosage form live up to the general principle of therapy noted above. This question needs to be studied through a comparison of the effects and adverse effects of the Enbrel 10 mg and 25 mg dosage forms.

(2) The Lack of Difference in Effects (Benefits of Therapy) Between 10 mg and 25 mg

A three-month comparative study of the two dose groups was conducted in a bridging study[1,2] on the efficacy of Enbrel in Japan, but the results of that study revealed no dose-response relationship or concentration-response relationship between the Enbrel 10 mg group and 25 mg group.

The lack of virtually any difference in efficacy between the 10 mg and 25 mg dosage forms can be explained in terms of Enbrel's mechanism of action. That is, since TNF occurs in excess amounts inherently greater than necessary in the living body, all that is needed by rheumatic patients suffering from exacerbated joint inflammation is the amount of Enbrel that is necessary for eliminating the excess TNF. The results of the above bridging study mean that, for most rheumatic arthritis patients, the necessary amount of Enbrel is not 25 mg, but 10 mg is enough.

(3) Adverse Effects of Enbrel

A. Common Adverse Effects of TNF-α Inhibitors

In a meta-analysis[4] of randomized comparative trials[3] (RCT) on TNF-α inhibitors (infliximab (brand name: Remicade) and adalimumab (brand name: Humira)) which are similar to Enbrel, it was reported that malignant tumors and infections definitely increased.[5]

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1 Studies which are conducted to verify that the results of overseas clinical trials are reproduced in Japanese individuals, the purpose of which is to make full use of overseas clinical trials so as to avoid redundant studies in Japan and to allow approval for good therapeutic drugs to be obtained sooner.

2 Etanercept approval application summary
http://www.info.pmda.go.jp/shinyaku/g050102/index.html?submit=%C9%BD%BC%A8

3 Studies in which subjects are randomly assigned to treatment groups (investigational product groups) and comparison groups (therapeutic drug groups, placebo groups, etc.) for evaluation in order to minimize data bias in studies and clinical trials, etc.

4 Systematic review in which the data from several clinical studies independently conducted in the past is collected and integrated for analysis by statistical methods.

B. Adverse Effects of Enbrel

No meta-analysis such as the above has been performed on Enbrel. However, in a recent integrated analysis of Enbrel, there were 1.92 adverse events in all, 3.12 serious adverse events, 1.69 infectious events (cases requiring antibiotic injection), and 2.43 medically important infections (other infections). All of these events were significant ($p < 0.0001$).

A dose-dependent increase in deaths from septic shock (the higher the risk of infection, the greater the harm due to worsening of infection) has also been reported. In particular, as noted below, the fact that serious reactions such as infection were significantly higher in the 25 mg and higher groups compared to the 10 mg group and placebo group is important, and in view of results indicating the significant development of malignant tumors due to anti-TNF-α antibodies such as infliximab and adalimumab, the risk of increases in malignant tumors should also be thoroughly considered with Enbrel as well.

C. Differences in magnitude of adverse effects (harm) between 10 mg and 25 mg dosage forms

A randomized trial comparing a placebo group and three Enbrel doses for the treatment of septic shock was conducted, and the mortality rates (%) after 4 weeks were compared. This randomized comparative study revealed a significant dose-response relationship between dose and mortality rate (%). That is, a dose-dependent increase in harm due to worsening infection was found in rheumatic patients with a high risk of infection.

(4) Appropriate Doses in terms of Risk-to-Benefit Ratio

As noted above, a greater dose of Enbrel than is necessary not only will not increase the effect but may also produce serious adverse effects such as the development of infection or malignant tumors because even the TNF-α needed for infection and tumor immunity is inhibited.

There is also virtually no difference in effect between Enbrel 10 mg and 25 mg, and for most people, 10 mg at a time may be enough as the dose of Enbrel needed to eliminate excess TNF-α in rheumatic patients. That is, excess Enbrel does not increase the effect but only results in harm.

Considered on the basis of the principle of the minimum needed for efficacy, the currently approved dosage of 25 mg in Japan is excessive to most rheumatic patients, and 10 mg should be necessary and sufficient.

3. Problem ②: Comparative study called for in conditions of approval not finished

(1) As noted in (1(1)) above, a condition of approval was that a "long-term (at least one year) double-blind comparative clinical study with appropriate control groups should be conducted in order to

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5 (Bongartz T, Sutton AJ, Sweeting MJ et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: JAMA. 2006;295:2275-85.)

6 (Fleischmann R, Baumgartner SW, Weisman MH et al. Long term safety of etanercept in elderly subjects with rheumatic diseases. *Ann Rheum Dis.* 2006; 65: 379-84.)

7 Fisher CJ Jr, Agosti JM, Opal SM et al. Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. N Engl J Med. 1996;334: 1697-702.

verify the efficacy, safety, and the like in preventing the progression of articular destruction during the administration of 10 mg and 25 mg, the results should be promptly reported, and the appropriateness of the Dosage and Administration should be reviewed." Only the 25 mg dosage form is currently in circulation and being used. As that study has not yet been completed, the efficacy and safety of 25 mg compared to 10 mg have not yet been sufficiently confirmed.

(2) However, as pointed out in the second section, there is no significant difference in the effects between the Enbrel 25 mg and 10 mg dosage forms, yet the adverse effects of the 25 mg dosage form appear to be greater. Under these circumstances, the circulation and use of only the 25 dosage form may have major adverse effects on the bodily safety of patients with rheumatoid arthritis.

(3) Therefore, at least until the efficacy and safety of the 25 dosage form are confirmed by the above comparative study, the method of administration should be changed so that, with the approval of the 10 mg dosage form, this 10 mg dosage form which may be expected to result in fewer adverse effects would be used as a general rule, while the 25 mg dosage form would in the meantime be given only to patients for whom the 10 mg dosage form appears to be ineffective or unsatisfactory, and healthcare professionals should be fully notified of this change.

(4) The above comparative study should also be completed as soon as possible, the efficacy and safety of the 25 mg dosage form should be promptly reviewed, and the results should be published.

4. Problem ③: All-Patient Surveillance

(1) Summary of All-Patient Surveillance

Wyeth conducted the post-marketing surveillance of all patients (all-patient surveillance) which was the first of the conditions for the approval of Enbrel.

The Japan College of Rheumatology Antirheumatoid Post-Marketing Surveillance Special Committee (PMS Committee) was established based on the wishes of the MHLW to obtain third party advice in conducting this surveillance (a "Contract for Medical Experts to Evaluate Safety of Enbrel" was drawn up on April 20, 2005 between the Japan College of Rheumatology and Wyeth KK for that purpose).[8]

The results of the all-patient surveillance are summarized below.[9]

Period: March 30, 2005 to April 27, 2007

Sample number: 13,894 cases

Evaluation: ① Out of the 13,894 cases, there were 4,336 adverse events (31.2%) over all, including 857 that were serious (6.17%) and 76 deaths (0.55%), and there were 3,714 adverse reactions (26.7%) overall, including 636 that were serious (4.58%) and 58 deaths (0.42%).

② There was a good response in cases also taking methotrexate (Rheumatrex).

③ The incidence of adverse events/adverse reactions decreased after the interim report.

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8 Japan College of Rheumatology homepage
"Statement on articles in The Mainichi Daily News and The Weekly Shincho" (April 2008)

9 Wyeth KK, Takeda Pharmaceutical Co., Ltd., Information on Proper Use of Enbrel, Advance Sheet (date unknown): excerpted from Report on Completion of All-Patient Surveillance.
http://www2.enbrel.jp/member/download/info_extra.pdf

④ The SMR[10] for these individuals compared to the mortality rate in general was 1.46, and considering the fact that the risk of death in patients with rheumatoid arthritis has been reported to be 1.5 to 2 times greater than in ordinary people, it would be difficult to conclude that the risk of death had increased.

(2) Problems in the Results of the All-Patient Surveillance

However, there are several problems, such as the following, in the results of the all-patient surveillance.

A. Report that "the SMR of 1.46 is on a par with the usual mortality rate for rheumatoid arthritis"

① The SMR of 1.46 is a comparison with the general population, but in this case, comparison must be made with a population that includes all terminally ill rheumatoid arthritis patients, including rheumatoid arthritis patients also suffering from cancer or stroke who did not use Enbrel.

However, 0.24% (17 out of 7,091 individuals) of rheumatoid arthritis patients had cancer in the all-patient surveillance. However, this is only 1/5 to 1/6 when compared to the fact that the percentage of patients with cancer is 1.4% (1,420,000 individuals), as calculated based on the 2005 patient surveillance. Also, the percentage of patients with cerebrovascular disease (which is 1,370,000, about the same number as cancer patients) in the general population is not shown in the all-patient surveillance. Similarly, the general population includes all dying or terminally ill patients, but it seems that no patients in poor condition were included in the patients in the all-patient surveillance.

There is thus a problem in the assessment that "the SMR of 1.46 is on a par with the usual mortality rate for rheumatoid arthritis."

② The SMR after the interim report is estimated to be 1.78 to 2.01.

In the interim report, the SMR was reported as 1.30, but the SMR had increased to 1.46 in the final report. This means that the SMR after the interim report had increased from 1.46.

Considered in terms of simple mortality, the mortality rate after the interim report was 1.55 times the rate in the interim report, and 1.55 times the SMR of 1.30 in the interim report would be 2.01. However, when similarly estimated based on a 1.22 multiplication factor with the overall SMR, the result would be 1.78. The SMR after the interim report may thus be between 1.78 and 2.01, and would be estimated to be far higher compared to the rate at the time of the interim report (SMR 1.30).

③ There may be other deaths than the reported deaths

In the final report on the all-patient surveillance, it was noted that the number of deaths were "cases in which adverse events/adverse reactions occurred during the observation period, and the outcome was death."

Based on those premises, there could be cases in which no adverse events/adverse reactions occurred during the observation period yet patients died. That is, it is possible that cases which should rightfully be considered adverse events were excluded.

B. Report that "there were fewer adverse events/adverse reactions after the interim report"

As pointed out in section A, there appear to be major problems with the reliability of the report on the mortality rate, and the assessment that the incidence of serious adverse events or serious adverse responses (adverse reactions) or the like was lower after the interim report is unacceptable as it stands.

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10 SMR (standardized mortality ratio) Shows the magnitude of mortality rates being compared, assuming a mortality rate of 100 for the population serving as a certain standard, and is used for comparison between populations or diseases.

Rather, in view of the fact that a comparison of patient characteristics during and after the interim report revealed an increase in the incidence (52.7% → 59.2%) of adverse reactions in the methotrexate co-administration group, it is possible that this affected the increase in the mortality rate.

It was also stated in the final report that a higher percentage was found to have a good response in the methotrexate co-administration group compared to the group that did not use methotrexate, but in this respect as well it is possible that the increase in the methotrexate co-administration group caused the increase in the mortality rate.

These points therefore need to be carefully considered, but there is no evidence of any additional examination from those standpoints in the all-patient surveillance.

C. Conflict of Interest

As noted above, the Japan College of Rheumatology contracted by Wyeth organized a special study committee to provide advice on the all-patient surveillance.

Article 8 in the contract between the two parties states that Wyeth will pay the association's "meeting expenses," "travel expenses," and "cost of accommodations." The committee members were actually reimbursed for travel expenses, daily expenses, and the like by the Japan College of Rheumatology, and the members were paid about 2,530,000 yen over a period of about 2 years through transfers from Wyeth into the association's account (a member of the American College of Rheumatology raised questions about conflict of interest on this point regarding the abstract prepared and published by the PMS committee at the Annual Conference of the American College of Rheumatology held in 2007 in Boston in the United States, and the American College of Rheumatology made inquiries to the Japan College of Rheumatology).

In light of the above relationship, the all-patient surveillance may be biased, and a more cautious approach to the assessments is therefore needed.

5. Problem ④: Process of Deliberation Regarding the Results of the All-Patient Surveillance

(1)The analysis of the all-patient surveillance on Enbrel was deliberated by the Pharmaceutical Affairs and Food Sanitation Council, First Committee on New Drugs, on April 27, 2007.[11]

At these deliberations, surveillance results such as those stating that "it was concluded that the onset and frequency of adverse reactions were not significantly different from those in the Japanese clinical study" were accepted at face value, and the condition of approval (conduct of all-patient surveillance) was terminated, without any particular discussion, on the grounds that "it has been determined that there are no significant problems at this time in terms of the safety and efficacy of the drug (Enbrel), and it is concluded that the details of Condition of Approval (1) could be confirmed."

(2) However, in addition to points that cannot be disregarded in terms of the adverse effects of Enbrel, there are major doubles about the reliability of the all-patient surveillance, as pointed out in 4 above. In particular, considering the fact that, even before the above deliberations, the PMS committee had confirmed there were 21 Enbrel treatment-related deaths among the total of 33 deaths out of the 7,091 subjects (interim report) in the all-patient surveillance, it should be said that more cautious deliberation was needed regarding the efficacy and safety of Enbrel, especially the effect on deaths.

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11 Minutes to meeting of the Pharmaceutical Affairs and Food Sanitation Council, First Committee on New Drugs "Deliberations on Results of All-Patient Surveillance (one of four conditions of approval)"

(3) However, it must be pointed out that the above deliberations on the effect of Enbrel and the results of the all-patient surveillance were only cursory, and that terminating the all-patient surveillance, particularly without any discussion of the deaths at all, is a significant problem (this also cannot be disregarded in light of the fact that, as a result of a PMDA special committee review of 60 of the 79 deaths which were reported by investigators as being Enbrel treatment-related, the PMDA then publicly reported, on December 6, 2007, that "16 were determined to be causally related to the use of the drug").

6. Conclusion

(1) Enbrel Dosage

There is virtually no difference in efficacy between Enbrel 25 mg and 10 mg, yet the adverse effects of 25 mg are significantly greater. From the standpoint of the risk-to-benefit ratio which is a significant principle of ethical drugs, the current 25 mg dosage form is excessive for most people, and a 10 mg to 5 mg dosage form would be sufficient.

(2) Approval of 10 mg Dosage Form and Its Use as a General Rule

At the present point in time, when the comparative study of the 10 mg and 25 mg dosage forms called for in the conditions of approval is still incomplete, the efficacy and safety of the 25 mg dosage formed cannot be said to have been sufficiently confirmed.

Therefore, until the efficacy and safety of the 25 dosage form are confirmed by the above study, the method of administration should be changed so that, with the approval of the 10 mg dosage form, this 10 mg dosage form which may be expected to result in fewer adverse effects would be used as a general rule, while the 25 mg dosage form would in the meantime be given only to patients for whom the 10 mg dosage form appears to be ineffective or unsatisfactory, and healthcare professionals should be fully notified of this change.

The above study should also be promptly completed, the results should be carefully and promptly reviewed, and the results should be published.

(3) Need for All-Patient Surveillance to be Reviewed Again

There are serious doubts about the reliability of the assessment of the mortality rate in the all-patient surveillance and the report on the incidence of adverse events/adverse reactions.

The deliberations leading to the termination of conditions of approval without a review of such problems must be said to be extremely inadequate.

The all-patient surveillance should be again reviewed in light of the perspectives pointed out in this demand, and the results should be publicly disclosed.

Attachments

Study Report on Efficacy and Safety of Etanercept (The Informed Prescriber, and the Non-Profit Organization Japan Institute of Pharmacovigilance) (March 2, 2009)

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