European Medicines Agency

London, 27 July 2006
Product name: REMICADE
Procedure number: EMEA/H/C/240/II/69

SCIENTIFIC DISCUSSION

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1. Introduction

Infliximab is a chimeric human-murine IgG1κ monoclonal antibody, which binds to both soluble and transmembrane forms of the human tumour necrosis factor (TNF)α and inhibits the functional activity of TNFα.

Remicade (infliximab) is currently approved for the treatment of rheumatoid arthritis (RA), Crohn's disease (CD), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis and ulcerative colitis (UC).

Infliximab was originally approved in August 1999 for a 2nd-line indication in CD, i.e. for use in patients after failure of corticosteroids and/or immunosuppressant therapies or in patients who are intolerant to or have medical contraindications for such therapies. In 2001, further to the 2nd annual re-assessment[1], the indication was restricted following an urgent safety restriction to 3rd line based on considerations of the total benefit/risk profile, particularly taking the limited knowledge of the safety profile of infliximab that was available at that time. The safety concerns pertained to tuberculosis (TB), other infections including sepsis, the potential risk for malignancies/lymphomas, fatalities, infusion reactions including anaphylactic reactions, and congestive heart failure.
Based on data from clinical trials (ACCENT 1, GETAID[2]), registry (TREAT[3]) and other post-marketing data, the MAH applied for a variation to extend the indication from 3rd to 2nd line in CD (section 4.1) and also proposed to revise the wording on strictures in patients with CD treated with infliximab (section 4.4).

2. Clinical aspects

To support this application the MAH referred to the data detailed below:

1) ACCENT I (C0168T21): multicentre, randomised, double blind, clinical trial of maintenance infliximab treatment compared with a single dose of infliximab in 580 patients with moderately to severely active CD.

2) GETAID: an investigator-initiated randomised, multicentre, placebo-controlled study to evaluate the combination of azathioprine/ 6-mercaptopurine (AZA/6-MP) in combination with infliximab as an induction regimen (3 infusions at 0, 2 and 6 weeks), compared with AZA/6-MP alone, in patients with steroid-dependent CD.

3) TREAT registry: on going commitment from the MAH, evaluating the long-term clinical, economic and quality of life outcomes of various treatment regimens, including infliximab, in the management of moderate to severe CD.

4) post-marketing data as assessed in the PSURs (periodic safety update reports).

2.1 Clinical efficacy

ACCENT I

The ACCENT I clinical trial was submitted and assessed within variation II.25 to support the maintenance therapy indication in CD. This variation received commission decision on 15 May 2003.

[1] The annual re-assessment consists of the review of the benefit/risk profile of the product based on the additional post-authorisation data (i.e. Specific Obligations) submitted to the EMEA.

[2] GETAID: Groupe d'étude thérapeutique des affections inflammatoires du tube digestif
[3] TREAT: Crohn's therapy resource evaluation and assessment tool registry

Summary of clinical efficacy

The study participants were adults above 18 years of age with a CDAI (Crohn´s disease activity index) of between 220 and 400 (moderately to severely active disease). The median age of the patients was 35 years, 58% were women. Duration of CD was 7.9 years, 57% had ileocolonic disease, in 24% and 19% was the disease located in the ileum and colon, respectively, 51% had previous segmental resections and 58% had extra-intestinal manifestations. Of note, patients were excluded for local manifestations of CD (e.g., strictures, abscesses, or other disease complications at screening) for which surgery might have been indicated.
The primary objective of the study was to examine whether patients responding 2 weeks after a single 5 mg/kg infusion of infliximab benefited from further treatments 2 and 6 weeks later followed by treatments every 8 weeks, compared with placebo treatment following the initial infusion. All patients received an initial dose of 5 mg/kg of infliximab at week 0. At week 2, patients were randomly assigned to one of three treatment groups: placebo infusions at weeks 2 and 6, and then every 8 weeks thereafter until week 46 (episodic strategy); 5 mg/kg infliximab infusion at the same time points (5 mg/kg scheduled maintenance strategy); or infliximab 5 mg/kg at weeks 2 and 6 and then 10 mg/kg every 8 weeks thereafter through week 46 (10 mg/kg scheduled maintenance strategy).
Patients who did not respond to the initial infusion were randomised separately from those who responded to the initial infusion. Patients who responded to treatment and subsequently lost their response were eligible to cross over to active episodic re-treatment.

The rate of response to the initial infusion of infliximab was about 60%. In the responders, after the initial infusion of infliximab the remission rates at week 30 and 54 as well as time to loss of response were significantly higher in patients receiving maintenance treatment with infliximab compared with placebo infusions. However, the efficacy mainly reflected differences in clinician interventions (change in medication, mostly corticosteroids) between the groups and not decrease in CDAI score. On the other hand these interventions are of clinical relevance for the condition and therefore acceptable as measures of clinical efficacy. For most endpoints, the infliximab 10 mg/kg group seemed to be superior to the 5 mg/kg dose, but differences did not reach statistical difference.

GETAID

The GETAID study was submitted as a manuscript (*Lemann et al*) for publication, therefore, no narratives, raw data, etc., were available for assessment.

Study participants, treatment and endpoints

This was a 12-month study designed to evaluate the value of an induction regimen of infliximab (week 0, 2 and 6) combined with AZA or 6-MP in steroid dependent CD patients. The aim of the study was to compare the rate of corticosteroid free remission.
The 113 study participants were randomised to treatment in two groups: group A (n=57) was treated with AZA at a daily dosage of between 2 and 3 mg/kg/day (or with 6-MP at a dose of 1 to 1.5 mg/kg/day) combined with infliximab infusion at 0, at 2, and at 6 weeks, at the dosage of 5 mg/kg; group B (n=56) was treated with AZA at the daily dosage of between 2 and 3 mg/kg/day, (or with 6-MP at a dose of 1 to 1.5 mg/kg/day) combined with a placebo infusion at 0, at 2, and at 6 weeks. Patients were also treated with steroids ≥ 10mg.

Two strata of patients were defined: the naïve stratum, consisting of patients that had not received AZA or 6-MP in at least 2 years; and the failure stratum consisting of patients who have failed AZA or 6-MP, despite receiving AZA/6-MP for more than 6 months at a stable and appropriate dose.

The primary efficacy endpoint was clinical remission (CDAI<150) off steroids at week 24. An additional 6-month follow-up period was included. Secondary endpoints were (a) success rate at week 12; (b) rate of steroid resistance (c); cumulative dose of prednisone at week 24; (d) steroid side effects

score at weeks 6, 12, and 24; and, (e) endoscopic improvement between inclusion and week 24, and (f) adverse events.

The patient population was between 22 and 38 years of age, and disease duration was longer in the placebo groups vs. infliximab (7 years vs. 5 years in the failure stratum, and 4 vs. 3 years in the naïve stratum), although this difference was not statistically significant.

Results

At week 24, the percentage of clinical remission was significantly higher in the infliximab group than in the placebo group (57% vs 29%; p=0.003). At weeks 12 and 52, the corresponding remission rates were 75% vs 38% (p<0.001) and 40% vs 22% (p=0.04), respectively. In each stratum (naïve or failure stratum), superiority of infliximab compared to placebo was found at week 12 for both strata, but significance was reached only for the naïve population at the primary endpoint, although a clear trend was observed for the failure population at week 24. Remission rate at week 52 was not statistically significant for either of the groups, although a trend in favour of infliximab was observed.

Steroid resistance was less common in the infliximab group than in the placebo group (5% vs 23%, or 5.1; 95% CI 1.3-19.2; p=0.01). Also for other secondary endpoints statistically significant benefit for the infliximab-treated patients was observed.

Discussion on clinical efficacy

The results of the ACCENT I study showed that infliximab is effective in maintaining a clinical response and clinical remission for up to 54 weeks in patients with moderately active CD who respond to a single infusion of infliximab. In addition, a corticosteroid sparing effect and improved quality of life were demonstrated. The results of the ACCENT I study did not support continued treatment with infliximab in patients not responding to a single infusion of infliximab. This finding is already addressed in the product information (PI) for infliximab.

The CHMP noted that the GETAID trial was designed to evaluate infliximab for achieving clinical remission off steroids in steroid-dependent CD patients, and not design to assess the safety of infliximab as 2nd line treatment instead of 3rd line. Furthermore, the study included only 3 infusions (at weeks 0, 2 and 6), therefore data from GETAID were considered of limited value for evaluating long-term benefit/risk in patients with moderately to severely active CD given maintenance treatment.

The request for supplementary information addressed the issue that data had not been presented to demonstrate that infliximab was comparable in terms of efficacy in 2nd line maintenance treatment of severe or fistulising CD to that of 2nd line agents (immunosuppressants or steroids). The MAH informed that there are no results from head-to-head trials but presented analysis that indicate that infliximab is at least as effective as the current 2nd line therapy, and this was accepted by the CHMP.

2.2 Clinical safety

ACCENT I

Summary of clinical safety

Exposure

The median cumulative dose of infliximab in this study was 9.7 mg/kg in patients randomised to the episodic strategy, 40.0 mg/kg in patients randomised to the 5 mg/kg scheduled maintenance treatment, and 64.9 mg/kg in patients randomised to the 10 mg/kg scheduled maintenance treatment.

Adverse events (AEs), serious AE (SAEs) and deaths

The individual AEs that were reported in the highest proportions of all randomised patients were headache (29%), upper respiratory tract infection (28%), abdominal pain (28%), nausea (23%), arthralgia (17%), (worsening of) CD (17%), pain (16%), pharyngitis (15%), rash (14%), vomiting (14%), dizziness and fever (13% each), fatigue (13%), sinusitis (11%), diarrhoea and insomnia (10% each). All other AEs were reported in less than 10% of all randomised patients.

Approximately two-thirds of the AEs reported as infections were treated (in 33% of all randomised patients) and the most frequent treated infection was upper respiratory tract infection (7%), followed by sinusitis (5%), pharyngitis (5%), bronchitis (4%), abscess and urinary tract infection (3% each), and moniliasis (3%). All other AEs recorded as a treated infection occurred in very small numbers of patients and had no discernible pattern.
Infections that were serious did not occur with any particular pattern and the only serious infection reported in more than 2 randomised patients overall was abscess, reported in 8 patients (4 in the placebo maintenance group, 3 in the 5 mg/kg maintenance group and 1 in the 10 mg/kg maintenance group). As reported through 30 weeks, 1 patient had a diagnosis of TB during the study. No other opportunistic infections for this population were identified through the end of the study.

The proportion of patients in the ACCENT I study with symptomatic intestinal obstruction, stricture, or stenosis (SSOs) was similar in all treatment groups despite a marked difference in the amount of infliximab used in each group. Symptomatic SSOs were reported in 6% of patients who received episodic treatment, 5% of patients who received 5 mg/kg infliximab scheduled strategy, and 6% of patients who received 10 mg/kg infliximab scheduled strategy.

Four patients died (3 died during the study and 1 died after study completion): 1 (10 mg/kg infliximab maintenance) of septic shock, 1 (10 mg/kg infliximab maintenance) of sepsis 144 days after the last study infusion, 1 (5 mg/kg infliximab maintenance) of myocardial infarction 25 days after the last study infusion, and 1 (placebo maintenance) of natural killer (NK)-cell lymphoma (for which death occurred after study completion). The events (septic shock, sepsis, and myocardial infarction) leading to these deaths were judged to be probably not related to study agent. The event, NK-cell lymphoma, was judged to be possibly related to the study agent.

GETAID

Since this was an investigator-initiated study that has been presented by the MAH as a manuscript for publication, safety information was only limited.

Exposure

In the GETAID study, 57 patients of 115 patients randomised were exposed to an induction regimen (3 doses) of infliximab.

AEs, SAEs and deaths

Frequency and severity of adverse events were not different between the two treatment groups. The percentages of patients who had at least one adverse event were 51% in the infliximab group and 50% in the placebo group. The frequency of infection was similar in the two treatment groups. Five serious adverse events were considered probably or possibly related to AZA: severe vomiting (n=1, infliximab group), arthralgia/myalgia/diarrhoea/fever (n=1, placebo), arthralgia/fever/cutaneous rash (n=1, placebo), pancreatitis (n=2, placebo). All patients discontinued AZA and recovered. One additional case of pancreatitis occurred in the infliximab group at week 26, during the follow-up period; AZA was stopped, but the cause remained unclear, as biliary stones were also found. One patient in the infliximab group had a severe reaction after the second and third infusions. The patient

recovered with steroids and adrenaline. No malignancy and no death occurred among the study patients.

TREAT

The MAH has an on going commitment to continue the TREAT patient registry and to provide regular reports to the EMEA/CHMP. Reports are provided on a yearly basis.
Exposure

Based on the data evaluated in April 2005, of the total of 6290 TREAT patients, around 51% (3235 patients) had been treated with infliximab. These patients received infliximab within 12 weeks prior to registration, were scheduled to receive infliximab within 30 days of registration, or received infliximab at some other point in the registry. Further to the request for supplementary information and at the oral explanation the MAH presented revised updated figures. Of the 6273 adult CD patients enrolled as of February 2006, a total of 3300 (around 53%) were treated with infliximab.

Approximately 25,000 infliximab infusions have been collected in the TREAT registry, with an infusion reaction rate of 4% of infusions (whereof 0.11% serious). The overall rate of infusion reactions was consistent with the rate observed in completed clinical trials of infliximab.
Demographic characteristics were balanced between the infliximab-treated patients and the patients who received other treatments. However, at the time of the TREAT registration, a greater percentage of infliximab-treated patients had moderate–severe or severe–fulminant CD as compared to the patients in the other treatment groups. Infliximab-treated patients were also more likely to have been hospitalised in the year prior to TREAT registration, and were more likely to have undergone surgery in the previous year. A greater percentage of infliximab-treated patients were taking prednisone at registration and infliximab-treated patients were also more likely to be taking concomitant immunomodulatory drugs (AZA, 6-MP, methotrexate, and cyclosporine). In addition, these patients reported worse overall health than CD patients enrolled in TREAT who did not receive infliximab.
The mean age of infliximab patients is around 40 years.

AEs, SAEs and deaths

From the data evaluated in April 2005, the most frequently reported adverse events[4] were gastrointestinal (65 vs. 43), with, abdominal pain as the most commonly reported event (16 vs. 12). Patients also frequently experienced diarrhoea (12 vs. 11) and exacerbation of CD (12 vs. 7).

Other body systems that had at least 2 events per 100 patient-years included: allergic and/or infusion reaction (8 vs. 1), cardiovascular (2 vs. 1), haematologic (8 vs. 5), resistance mechanism / infection (6 vs. 3), respiratory system (3 vs. 1), and skin and appendages (4 vs. 1).

Further to the request for supplementary information the MAH provided subgroup analysis based on duration of treatment, intervals of administration, availability of data and 2nd line vs. 3rd line treatment.

Without adjustment to other factors, there was a higher rate of serious infection within 3 months of infliximab infusion compared with patients who had never received infliximab or had not received it in the prior 3 months. The same was observed when comparing intermittent vs. maintenance treatment. However, when multivariate adjusted analysis (for age, CD severity and use of other medications) was carried out, infliximab was not considered as a predictor of serious infection.
There were no cases of TB reported in any patient in either group in the TREAT Registry.

Based on the data provided in April 2005, a total of 74 neoplasic events were reported. The incidence of cancer was similar in the infliximab-treated patients when compared to the patients who had received other CD treatments only. Further to the request for supplementary information, the MAH

[4] The figures are presented as infliximab treated vs. other treatments only. They are based on an analysis per 100 patient-years.

provided an updated analysis for non-melanoma skin cancer, which was not initially included in the analysis of estimation of malignancy risk. The MAH provided revised figures at the oral explanation. The incidence per 100 patient-years for all cancers was 0.74 of infliximab treated patients vs 0.82 for patients that received other CD treatments. When looking at lymphoma, the incidence was 0.07 vs 0.08, respectively. At present, data from the TREAT registry do not demonstrate an increased risk of malignancy with infliximab treatment compared to other treatments. However, the CHMP noted that the follow-up period is still relatively short (approximately 2.5 years), and reiterated the need to maintain close follow-up of these patients. The potential tumour promoting effect of infliximab cannot be excluded and malignancies might require a certain time and also a prolonged exposure to infliximab to be triggered.

There were 101 occurrences of SSOs among infliximab-treated patients and 62 among patients in the other treatments only group. This difference in the unadjusted rate was statistically significant ($p<0.001$, unadjusted RR 1.0 for other treatments vs. 1.75 for infliximab, 95% CI 1.284 – 2.396).
Patients with refractory symptoms due to an already-existing SSOs could be more likely to be treated with infliximab.
The *Lichtenstein* group[5] performed a multivariate analysis on the data submitted in April 2004 for assessment and showed that while duration of CD, the severity of CD and CD isolated to the small bowel were independently associated with the development of SSO events, the use of infliximab was not, when adjusted for these and other potentially confounding factors. Based on the data from April 2005, using multivariate analysis for adjustment for potential confounding factors, infliximab use is not an independent predictor of SSO events.

Mortality rates were similar when the comparison was made between infliximab-treated patients and those having received other CD treatments only. Examination of the causes of death did not suggest a difference between the two groups. The MAH presented revised figures at the oral explanation. Deaths per 100 patient-years throughout the entire duration of the registry were 0.50 in the infliximab group and 0.54 in the other treatments only group. No statistically significant difference was observed.

Post-marketing experience

The PSUR 10 covered the period from 24 February 2004 to 23 August 2004. Cumulatively, 576,000 patients have been exposed to infliximab for a total of 1,347,000 person-years elapsed since first exposure. As the outcome of the assessment of this PSUR, the risk/benefit balance of infliximab remained positive. In general, the adverse event profile of infliximab was considered well characterised. Infliximab adds an extra risk for serious infections, including TB. Other adverse events under surveillance were e.g. serious blood reactions, in particular peniae, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), and liver failure. From the safety data submitted, it was concluded, that these serious conditions occur mainly in patients where other significant co-morbidities and significant other medications are present. In most cases the most plausible explanation was secondary to other complicating factors, where infections are the most commonly involved. Activation/reactivation of demyelinating disease is also recognised as a possible adverse event in patients treated with infliximab. No new signals were found within this PSUR period.
It was also noted that a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-blocking agent cannot be excluded.

Discussion on clinical safety

Safety data from the above-mentioned sources were discussed by the CHMP. At the time of the 2nd annual reassessment data in CD were very limited, and only short-term treatment was approved.

[5] *Lichtenstein GR, et al*, Assessment of infliximab and other factors as potential risks for the development of intestinal stricture, stenosis or obstruction in Crohn's disease – Data from the 6000-patient TREAT registry. Am J Gastro 2004; 99(10):S250.

Following the identification of several safety concerns, the indication was revised from 2nd line to 3rd line treatment in severe active, CD.
In May 2003 a type II variation for maintenance treatment in CD patients was approved. This was based mainly on the ACCENT I trial. A major limitation of the ACCENT I study in terms of safety results was the lack of a real placebo group since all patients received at least 1 infusion with infliximab. Within the placebo group 50% of the patients crossed over to active treatment and the re-treatment schedule made any dose response evaluations difficult. Therefore, there were not any differences in the total number of AEs and SAEs between the treatment groups. However, the safety results of the trial confirmed previous experience with infliximab and no new safety concerns were identified with regard to the previously known safety issues (infections, infusion reactions, delayed hypersensitivity reactions, autoimmunity, immunological and neurological disorders). With regard to malignancy, the incidence was 1% and this appeared high in the young patient group. However, no apparent consistency was observed in the type of malignancy. One lymphoma was reported.

For the present application the MAH submitted also the GETAID study. However, the safety information obtained for this study related to the short-term induction therapy regimen and because it was presented as a manuscript, some safety information, e.g. the exact nature of serious or severe events (including drug-related events) were not included. Notwithstanding this fact, no new safety findings were identified.

The data from the TREAT registry reflect the real-world use of the medicinal products for treatment of CD. The CHMP considered that the data presented are reassuring, as it confirmed the already known safety profile of infliximab, and it did not identify any new signals within the CD population. Additionally, the MAH provided evidence of at least a similar risk profile of infliximab compared with other medications used in CD. In addition, adjusted analyses presented by the MAH suggest that infliximab is not associated with an increased risk of death or infections.
The CHMP reiterated the need to continue with the follow-up of the registry. The MAH will continue to present annual updates for assessment.

The CHMP raised concerns regarding the findings related to 6 cases of a rare type of hepatosplenic T-cell lymphoma (HSTCL) identified in adolescent and young adult CD patients treated with infliximab and concomitant AZA or 6-MP that lead to the update of the product information in May 2006, via variation II.84. A causal relationship of HSTCL and infliximab therapy could not be excluded. The MAH was asked to address this issue in answers to supplementary information and at the oral explanation. The MAH gave feedback on an expert meeting held on 21st July 2006. Hypotheses were given for the development of this type of lymphoma, but no conclusions can be reached yet. However, the MAH informed on the efforts being developed on how to proceed with HSTCL, in specific the analysis of the possible role of registries and educational programs. Furthermore, the MAH informed that all reports of lymphoma are being reviewed in depth. This was noted by the CHMP.
Regarding stricturing in CD, the data from TREAT and ACCENT I did not indicade an increased risk for the development of strictures. Additionally, it there was no evidence that the administration of infliximab to patients with fibrotic strictures harms the patient, while there may even be some benefit for patients with inflammatory strictures. Further to a request for supplementary information the MAH provided data regarding experience with surgery. The data on experience with surgery indicate that infliximab or immunossupressive therapy do not increase the risk for postoperative complications such as infections. Data suggests that rapid mucosal healing is not accompanied with the development of strictures, although the patient number was considered low to draw any definite conclusions. The CHMP noted that only longer-term data from the TREAT registry might help to finally address this question.
Therefore, the CHMP proposed a revision of the initially submitted wording on strictures and recommended that the MAH committed to perform post authorisation follow-up measures to gather as information on strictures. The MAH agreed with the CHMP recommendation and submitted a revised letter of undertaking.

3 Overall discussion and benefit/risk assessment

The CHMP considered that the benefit of infliximab has been demonstrated in the intended patient population.
Furthermore, the safety concerns leading to the change in the indication from 2nd line to 3rd line in 2001 are at present characterised and followed through longer-term surveillance of subjects who participated in infliximab clinical trials in CD and through analysis of data collected in the registries.
The analysis from several clinical studies and registries provided demonstrated that no new safety concerns were observed and indicated that infliximab has comparative safety vs. the alternative treatments in severe CD. The maintenance of long-term follow up was considered important and recommended.
The CHMP also noted that flexibility in treatment of severe active CD is important. Therefore, 2nd line therapy with infliximab might be justified in certain clinical situations, e.g. where a patient with severe, active CD is not responding to high doses of steroids or as a add-on therapy initiated during the time that it may take for immunomodulators to exhibit full effect.

The CHMP expressed concern with the HSTCL cases, in particular with relevance to the paediatric population, since the 6 cases reported were in adolescent and young adult patients. The efforts developed by the MAH on how to proceed with HSTCL, in specific the investigation of the possible role of registries and educational programs for both prescribers and the patients were noted.

Given the larger experience with infliximab available now, both in terms of efficacy and safety in CD, as well as the ongoing educational activities and the current PI which reflects the safety profile of infliximab adequately, the CHMP considered that this variation was acceptable.

CONCLUSION

On 27 July 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and the Package Leaflet.