November 2003

Overview of anakinra reports

Introduction

Anakinra (Kineret®) was granted a market authorisation for Europe on 8 March 2002 by the European Commission. Anakinra is a human interleukin-1 receptor antagonist, indicated for *the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients with an inadequate response to methotrexate alone* [1]. It is administered daily by subcutaneous route. It's safety profile is dominated by allergic reactions, infections and neutropenia. The latter two especially occur with etanercept as co-medication[2].
The aim of this report is to summarise the reports as received by Lareb and to compare them with the SPC.

Reports

Between approval and the 2nd of July 2003, the Netherlands Pharmacovigilance Centre Lareb received 12 reports on 11 patients (table 1) of which one report (case B) was sent by a health professional directly.

Two *fatal* cases were reported. A male aged 68 died due to cardiac failure without prior history of cardiac disease (case A). A hypersensitivity component could not be clearly identified in the report. A female aged 62 died due to fatal sequelae after changing her tracheostoma, necessary because of herpes pneumonia (case E).
Three cases concerned *hypersensitivity*: Dyspnoea (case B), hypersensitivity with cardiac sequelae and oropharyngeal edema (case D), and injection site reaction with haemorrhagic diarrhoea (case J). In cases B and D, no immunosuppressive concomitant medication was reported.
Four cases with *infectious events* were reported: fatal herpes pneumonia (case E), septic shock (case F), pulmonary tuberculosis case G), and streptococcal sepsis with spondylodiscitis (case H). In cases F, G and H, methotrexate (MTX) was reported as concomitant medication.
One case (K) of *drug-induced thrombocytopenia* was reported with normal leukocyte count and haemoglobin level. Bone marrow depression, or etanercept as concomitant medication were not reported.
In all reports, rheumatoid arthritis was mentioned as indication.

Other sources of information

Databases

The WHO database contains 174 associations with anakinra. Associations with >3 reports do not reveal unexpected events (table 2).

Table 1. reports on anakinra

patient, gender, age	reporter	first admin. last admin. eventdate	other suspect medication	co-immuno-suppression	co-medication	event outcome remarks
37783 A F, 68	Amgen	25-6-2002 5-7-2002 5-7-2002		azathioprine 100 mg/d, prednisone	ibuprofen	- cardiac failure, death due to cardiac decompensation - fatal - no history of cardiac decompensation or cardiovascular risk factors
37975 B, M, 60	specialist	medio Sept ?? medio Sept			carbasalate calcium 38 mg, clopidogrel 75 mg, diclofenac 25 mg, perinopril 4 mg, furosemide 2dd 40 mg, bisoprolol 10 mg, isordil 5 mg as necessary, simvastatine 40 mg	- dyspnoea - recovered after withdrawal - no cardiological or pulmonal explanation could be found
38201 C F, 35	Amgen	15-5-2002 17-8-2002 Aug 2002	OAC	MTX 25 mg/week	rofecoxib 25 mg/d,folic acid 5 mg/d, omeprazole 20 mg/d, pantoprazole 40 mg/d, metoclopramide, temazepam 10 mg/d	- Budd Chiari syndrome, Protein C deficiency, systemic lupus erythematosus - surgical intervention - preexisting ?
38551 D F, 55	Amgen	5-6-2002 17-6-2002 7-6-2002			sotalol 2dd 80 mg, simvastatin, acenocoumarol, sulfasalazine, diclofenac, losartan, diltiazem	- hypersensitivity, ventricular extrasystoles, collapse, chest discomfort, tonque oedema, pharyngolaryngeal pain - recovered after withdrawal - no cardiac explanation for symptoms, similar reaction on previous etanercept, history: SLE, VES, malignant breast neoplasm
39341 E F, 62	Amgen	11-7-2002 18-10-2002 3-11-2002	prednisone		acetylsalicylate calcium, rofecoxib, fosinopril	- pneumonia herpes viral, tracheostomy malfunction, respiratory failure, myocardial infarction, leukopenia, death - fatal - history of COPD, changing of the tracheostoma caused fatal sequelae, previously treated with leflunomide and infliximab
39913 F F, ?	Amgen			MTX		- septic shock - ? - history of diabetes mellitus
39927 G M, 69	Amgen	22-5-2002 5-2-2003 26-1-2003		MTX	folic acid, bisacodyl, pantoprazole, sulfasalazine	- pulmonary tuberculosis - recovered - history of diabetes mellitus, aortic dissection, hypertension, no risk factors identified for TBC

patient, gender, age	reporter	first admin. last admin. eventdate	other suspect medication	co-immuno-suppression	co-medication	event outcome remarks
39930 H F, 74	Amgen	3-6-2002 13-2-2003 10-2-2003	MTX	MTX	diclofenac 100 mg/d, folic acid 0,5 mg/d, misoprostol 400 microgram/d, acebutolol 200 mg/d, enalapril 5 mg/d, amitryptiline 10 mg/d, cinnarazine 25 mg/d	- streptococcal sepsis, osteomyelitis, (spondylodiscitis) - ? - onset two days after dental surgery with local anaestesia
40066 I F, 52	specialist	00-10-2002 00-4-2003 ??			meloxicam, folic acid, paracetamol	- eczema - ? - ?
40222 J F, 33	Amgen	5-2-2003 21-2-2003 19-2-2003		MTX	diclofenac, misoprostol, folic acid, calcium carbonate, paracetamol	- injection site reaction (positive rechallenge), diarrhoea haemorrhagic, pharyngolaryngeal pain, headache, paraesthesia - ?
40828 40851 K,F,64	Amgen	17-2-2003 13-5-2003 12-5-2003			diclofenac, misoprostol, omeprazole 40 mg/d	- thrombocytopenia, bruising - recovered after withdrawal and steroids - platelets 8 * 10^9/L

In all cases, rheumatoid arthritis was mentioned as indication for anakinra. MTX: methotrexate

Table 2. associations with anakinra in the WHO-database with >3 reports

ADR	n	ROR	CI_{95}
leg pain	4	32.8	11.9-90.8
injection site reaction	19	22.6	13.1-39.3
injection site pain	6	15.4	6.6-35.8
rash erythematous	5	3.5	1.4-8.8
pruritus	4	1.6	0.6-4.5
fever	4	1.5	0.6-4.2

Conclusion

Two out of twelve reports have been received from a health professional.

The profile of the reports fits within the safety profile as described in the SPC. The two fatal cases stress that monitoring of this drug is indicated.

References

1. EMEA. Dutch SPC of Kineret. (version date 15-4-2002) http://www.eudra.org.
2. EMEA. EMEA Public Statement. Increased risk of serious infections and neutropenia in patients treated concurrently with Kineret (anakinra) and Enbrel (etanercept). (version date 5-2-2003) http://www.emea.eu.int.