Knowledge creation about ADRs – turning the perspective from the rear mirror to the projector?

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

- Serious and unexpected adverse drug reactions (ADRs) have been reported shortly after marketing of a number of drugs.
- Review of ADR cases by the regulatory authorities has resulted in suspension of drugs or restrictions in product information.

WHAT THIS STUDY ADDS?

- Information about serious and unexpected ADRs of three drugs with reported serious ADRs was already present in the registration files.
- Observations of these ADRs were not investigated further before marketing.
- A more active utilization of the ADR information in premarketing studies could probably prevent the appearance of unexpected and serious ADR cases after marketing.

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AIMS

Spontaneous reports of adverse drug reactions (ADRs) are often the only documentation used to justify the recall of drugs from the market. The purpose of this study was to investigate whether it would have been possible to foresee serious ADR cases based on available information on ADRs reported in Phase II and III clinical trials before marketing.

METHODS

We conducted a retrospective analysis of reported ADR data in Phase II/III clinical trials in the registration material for three different ADR scenarios: (i) trovafloxacin/ alatrofloxacin and hepatotoxicity; (ii) tolcapone and hepatotoxicity and neuroleptic malignant syndrome; and (iii) rituximab and cytokine release syndrome. We chose the scenarios because they were of serious character and caused great damage to the patients and because of different outcomes of the scientific discussions in the regulatory agencies.

RESULTS

In all three cases, the registration material contained observations of ADRs, but there had been no follow-up on these observations. ADRs were mentioned in the summary of product information (SPC) purely as information, to some extent accompanied by recommendations. The information was not converted into new knowledge and remained tacit knowledge embedded in the SPCs disseminated to health professionals/prescribers.

CONCLUSIONS

The registration material analysed contained information about ADRs that were reported later, meaning that it would have been possible to foresee the occurrence of the ADRs at the time of licensing. More active utilization of the information from Phase II/III clinical trials is recommended to prevent the appearance of unexpected ADRs and further emphasis in SPC warnings to doctors about possible serious ADRs.

Introduction

The thalidomide scandal at the beginning of the 1960s led to greater focus on drug safety. Statutory requirements on documenting the efficacy and safety of new drugs were reinforced, and systems were established for reporting spontaneous adverse drug reactions (ADRs) after drugs had been marketed [1]. Despite rigid requirements for documenting the ADR profiles of new drugs, reporting of unexpected ADRs does occur after marketing of the drugs, resulting in drug recalls.

There are numerous examples of this: mibefradil was recalled in 1998 due to new information about potentially harmful interactions with other drugs [2], and sertindole was temporarily suspended from the market in December 1998 due to concerns over the risk of cardiac arrhythmia and sudden death [3]. Recently, the recall of rofecoxib from the market in 2004 due to new data about increased risk of cardiovascular problems attracted worldwide attention [4].

A review of the literature [5] has documented that spontaneous reports of ADRs are often the only form of evidence used as a basis for recalling drugs when serious ADR cases emerge after licensing of the drugs. Often, serious ADRs are reported anecdotally or as small case series, and this amount of evidence is often considered to provide convincing evidence of a causal association that does not need further verification [6]. The literature review [5] did not document whether information on the later reported ADRs was reported in the clinical development trials or, if so, whether this information was considered in the assessment of the ADR cases.

The purpose of this study was to investigate whether it would have been possible to foresee serious ADRs based on information reported in the clinical trials before marketing of the drugs.

Methods

Design

A retrospective evaluation was conducted of the ADR data from the registration material for three selected drugs where serious cases of ADRs had been reported shortly after licensing of the drug to explore whether symptoms of the analysed ADR cases were reported in the clinical trials.

Selection of cases

The drugs were approved through the central procedure in the EU. Reports of serious ADRs that occur after marketing of the drug are discussed in the EU's central body for drug safety: Central Human Committee of Medical Products (CHMP) and the Pharmacovigilance Working Party (PhWVP).

The European Medicines Agency (EMA) registers all problems of safety in relation to human drugs discussed in

the EU. As of November 2006, 277 different safety problems had been reported for specialized human drugs and herbal drugs in the EU. The safety problems reported represent a broad spectrum of major and minor ADR cases, all discussed in the PhWVP and the CHMP. Three ADR scenarios were selected from those ADR cases discussed that resulted in: (i) suspension of marketing authorization, (ii) suspension and later cancellation of suspension due to new ADR data, or (iii) restrictions in the summary of product information (SPC), as these three categories represent the classic end-results of the regulatory authorities' assessment of an ADR case.

ADR scenarios

The following drugs and ADR scenarios were selected as the subjects for analysis:

- 1 Trovafloxacin/alatrofloxacin and hepatotoxicity.
- 2 Tolcapone and hepatotoxicity; neuroleptic malignant syndrome.
- 3 Rituximab and cytokine release syndrome.

The specific scenarios with hepatotoxicity, neuroleptic malignant syndrome and cytokine release syndrome were chosen because they were of serious character and caused great damage to patients.

The scenarios also represented three different treatment areas: infection, Parkinson's disease and cancer treatment, respectively. Table 1 contains a detailed description of the progress of the ADR scenarios, and also contains an overview of the indications for which the drug was approved in the EU, and the regulatory steps taken in connection with assessing cases in the EU. Table 1 also contains an estimate of the number of patients receiving treatment with the drugs after marketing in the EU and the USA.

Materials

The following materials were used in the analysis of the ADR cases:

- Registration files
- Summary of product information
- Assessment reports of the registration files made by the rapporteur member state and the corapporteur member state during the central approval procedure.

The registration material was collected from the Danish Medicine Agency's archives, in which all original material is stored. The process of sorting, data extraction and analysis was extensive because of the volume of the material, ~20 filled storage boxes. The registration applications predate the year 2000, and thus were not accessible electronically, meaning that all extraction was carried out manually.

Table 1

Adverse drug reaction (ADR) cases

Drug/ drug class	Proven indication(s)	Approval time in EU	Regulatory actions in EU	ADR case description	No. of people treated after market authorization	Ref.	Market authorization holder
Trovafoxacin/ alatrofloxacin (Trovan)/ antibiotic, fluoroquinolone	Community acquired pneumonia Nosocomial pneumonia Acute bacterial exacerbation of chronic bronchitis Acute uncomplicated urinary tract infection Sexually transmitted diseases Acute pelvis infections Surgical prophylaxis Skin and skin structure infections Meningococcal meningitis	July 1998	Suspended from market in June 1999	152 documented ADR reports on serious hepatic events including 9 cases where patients died or required a liver transplant All deaths were reported in the USA. The liver damage occurred from 1 to 60 days after treatment start The review showed that in 35% of these cases, the reported liver/biliary events were accompanied by a hypersensitivity reaction or in other cases hepatotoxicity ADR hypersensitivity is a type of reaction that may occur with increasing frequency as more patients become re-exposed Comparative US spontaneous reporting data provide a strong signal that the ADRs are more frequent and more severe compared with other quinolones and other antibiotics The results of the review indicated that it was not possible to identify a single indication where the therapeutic benefit would outweigh the occurrence of severe, serious and unpredictable hepatic damage associated with the use of trovafoxacin/alatrofloxacin	2500 000 prescriptions worldwide 200 000 prescriptions in the EU since the authorization	[7, 8]	Pfizer Ltd/Roerig Farmaceutici Italiana S.R.L.
Tolcapone (Tasmar)/ antiparkinsonian catechol-o-methyl-transferase inhibitor	Parkinson's disease	September 1997	Suspended from the market in November 1998 Reintroduced in April 2004	96 ADR reports of hepatotoxicity and 6 cases of neuroleptic malignant syndrome including rhabdomyolysis and hyperthermia Roche conducted new clinical trials that rejected a connection between the use of Tolcapone and the reported ADRs Tasmar legal status was also restricted to prescription by physicians experienced in the management of advanced Parkinson's disease On the basis of these evaluations, the CHMP agreed to lift the suspension of the marketing authorization in April 2004	Around 100 000 patients were treated with tolcapone from 1997 to 1998	[9]	Roche

Table 1
Continued

Drug/ drug class	Proven indication(s)	Approval time in EU	Regulatory actions in EU	ADR case description	No. of people treated after market authorization	Ref.	Market authorization holder
Rituximab (MabThera)/ antineoplastic, immunological agent Monoclonal antibody	Low-grade or follicular B-cell lymphoma that is resistant or patients in their second or subsequent relapse after chemotherapy Orphan Drug Status for use in the treatment of non-Hodgkin's B-cell lymphoma	November 1998	Limitations in the indications 1999	Eight ADR cases of cytokine release syndrome with fatal outcome At least three of these cases were in patients treated for indications other than follicular lymphoma These fatal reactions developed early in the first infusion, particularly dyspnoea, accompanied by severe bronchospasm and/or hypoxia CHMP evaluated that further clinical trials were unnecessary, and decided to set out restrictions in the SPC	Estimated: 12 000–14 000 patients have been treated with rituximab worldwide since authorization in the USA in November 1997 and in the EU in June 1998	[10]	Roche

Data extraction and handling

The object of the analysis was all ADR data reported in Phase II and III clinical trials. Only ADR data from Phase II and III is included in the analysis, as these data represent information about ADRs, which are published in the product information at the time of marketing. ADR data from Phase I trials, including interaction studies, distribution and metabolism studies and bio-accessibility studies, were excluded. ADR data from postmarketing studies were not included in the files and not studied in this paper.

A characterization of the Phase II and III clinical trials was made for the analysis of reported ADRs. The clinical trials were characterized by the following taxonomy inspired by general guidelines for pharmacoepidemiological research [11]: study design, dosage range and exposure time. Characteristics of included patients (number, age, diseases, comparator drugs and study settings) were also extracted.

ADR data reported in the clinical studies and presented in the registration files were extracted for each case. Detailed information about the reported ADRs for each clinical trial cannot be given, as data are not provided in an accessible manner in the registration files.

If knowledge of the explored ADR cases was reported in the registration application, the extent to which the SPC contained information about these ADRs was evaluated, and whether the information was accompanied by warnings or recommendations for healthcare professionals. Only the initial SPCs released at the time of marketing were evaluated.

Definitions

In the study a distinction is made between the concepts 'information about' and 'knowledge about' ADRs, as follows. Information is data in its purest form. Information provides a new point of view for interpreting events or objects, making visible previously invisible meanings or shedding light on unexpected connections [12]. Knowledge is information that is tested, confirmed, anchored and internalized [12].

Results

Table 2 shows an overview of the Phase II/III clinical trials included in the registration material for trovafloxacin, tolcapone and rituximab.

The presentation of the data in the Results section will reflect the fact that the reporting form differs from drug to drug. We have maintained the reporting form of the registration material used.

Trovafloxacin/alatrofloxacin

Oral trovafloxacin and i.v. alatrofloxacin were investigated in five Phase II and 29 Phase III clinical trials, including 6636

Table 2a

Overview over clinical phase II and III trials in registration files

Study	Study design	Trovafoxacin/ alatrofoxacin	Comparator drug	Duration of treatment (days)	No. of treated/comparator/age*	No. of centres	Included patients
Trovafoxacin							
1. Lower respiratory tract infections:							
Community-acquired pneumonia							
1A	Phase II – R, DB, MC, DD study	200 mg/300 mg trovafoxacin od	Cefaclor 500 mg tid	10	102/47/18–73 years	18	CAP (uncomplicated, outpatient)
1B	Phase III – R, MC, DB, DD study	200 mg trovafoxacin od	Amoxicillin 500 mg tid +/- erythromycin	7–10	150/152/16–95 years	45	CAP
1C	Phase III – R, MC, DB, DD study	200 mg trovafoxacin od	Clarithromycin 500 mg bid	7–10	178/180/17–88 years	51	CAP
1D	Phase III – R, DB, MC study I.v. to oral therapy	Alatrofoxacin i.v. 200 mg to trovafoxacin 200 mg	Ciprofloxacin 400 mg bid + ampicillin 500 mg qid i.v. Ciprofloxacin 500 mg bid + ampicillin 500 mg tid p.o.	7–10	196/110/17–94 years	42	CAP (requiring hospitalization)
1E	Phase III – R, MC, DB, DD study I.v. to oral therapy	Alatrofoxacin i.v. 200 mg to trovafoxacin 200 mg	Ceftriaxone 1 g od i.v. Cefpodoxime 200 mg bid p.o. +/- erythromycin	7–10	111/222/16–95 years	68	CAP (requiring hospitalization)
2. Nosocomial pneumonia							
2A	Phase III – R, MC, DB, DD study	Alatrofoxacin i.v. 300 mg to trovafoxacin 200 mg +/- aztreonam +/- vancomycin	Ciprofloxacin 400 mg bid i.v. 750 mg bid p.o. +/- aztreonam +/- vancomycin +/- clindamycin/ metronidazole	10–14	127/137/20–98 years	84	Nosocomial pneumonia
2B	Phase III – R, MC, O study	Alatrofoxacin i.v. 300 mg to trovafoxacin 200 mg +/- vancomycin	Ceftazidime 2 g bid i.v. Ciprofloxacin 750 mg bid p.o. +/- vancomycin +/- gentamicin	10–14	135/140/18–92 years	62	Nosocomial pneumonia
3. Acute exacerbations of chronic bronchitis (AECB)							
3A	Phase II – R, DB, DD study	Trovafoxacin 100 or 300 mg od	Ofloxacin 400 mg bid	10	148/73/18–78 years	28	AECB >40 years
3B	Phase III – R, MC, DB, DD study	100/200 mg trovafoxacin od	Amoxicillin 500 mg tid	5	279/132/40–94 years	56	AECB >40 years
3C	Phase III – R, DB, MC study	100 mg trovafoxacin od	Clarithromycin 500 mg bid	7	210/200/40–88 years	54	AECB >40 years
3D	Phase III – R, MC, O study	100/200 mg trovafoxacin od from 3 to 7 days	Amoxicillin/clavulanate (500/125 mg tid)	5	279/140/40–92 years	111	AECB >40 years; FEV ₁ /FVC <70%
3E	Phase III – R, DB, MC study	100 mg trovafoxacin od	Ciprofloxacin 500 mg bid	7	131/125/40–88 years	22	AECB >40 years
4. Sinusitis							
4A	Phase III – O, MC study	200 mg trovafoxacin od	None	10	254/0/16–82 years	16	Acute sinusitis
4B	Phase III – R, DB, DD, MC study	200 mg trovafoxacin od	Clarithromycin (500 mg bid) 14 days	10	203/214/16–82 years	39	Acute sinusitis
4C	Phase III – RA, MC, O study	200 mg trovafoxacin od	Amoxicillin/clavulanate (500/125 mg tid)	10	205/209/17–83 years	68	Acute sinusitis
5. Urinary tract infections: acute, uncomplicated							
5A	Phase II – R, DB, DD, MC study	Trovafoxacin 100 mg od/bid	Ciprofloxacin 250 mg bid	7	146/75/21–75 years	16	Uncomplicated urinary tract infections
5B	Phase III – R, DB, MC study	Trovafoxacin 100 mg od/bid	Norfloxacin (400 mg bid)	3–7	364/178/16–86 years	34	Uncomplicated acute urinary tract infections
6. Prostatitis							
6A	Phase III – R, MC, DB, DD study	Trovafoxacin 200 mg od	Ofloxacin 300 mg bid 42 days	28	NA, 19–94 years	59	

7. Sexually transmitted diseases							
7A	Phase II – R, O dose ranging study	Trovafoxacin 50, 100, 200 mg od	None	7	130/–/18–43 years	2	Uncomplicated chlamydia urethritis/cervicitis
7B	Phase II – R, O dose ranging study	Trovafoxacin 50 mg, 100 mg or 200 mg single dose oral	None	NA	311/314/18–46 years	1	Gonorrhoea
7C	Phase III – R, MC, DB, DD study	Trovafoxacin 100 mg single dose	Ofloxacin (400 mg) single dose	NA	311/314/16–62 years	10	Gonorrhoea
7D	Phase III – R, MC, DB, DD study	Trovafoxacin 200 mg	Doxycycline 100 mg bid	5	489/481/15–60 years	41	Uncomplicated chlamydia urethritis/cervicitis
8. Pelvic inflammatory disease							
8A	Phase III – R, MC, DB, DD study	Alatrofloxacina 200 mg i.v. Trovafoxacin 200 mg	Cefoxitin 2 g/6 h + doxycycline 100 mg/12 h both i.v. Doxycyclin 100 mg bid	14	79/79/16–47 years	41	Acute PID
8B	Phase III – R, MC, DB, DD study	Trovafoxacin 200 mg	Ofloxacin 400 mg bid + clindamycin 450 mg qid	14	149/156/16–56 years	57	Acute PID (outpatient)
9. Surgical and pelvic infections							
9A	Phase III – R, DB, MC study	Alatrofloxacina 300 mg i.v. Trovafoxacin 200 mg	Cefoxitin 2 g/6 h Amoxicillin/clavulanate 500/125 mg tid p.o.	<14	160/157/14–71 years	58	Acute pelvic infection
9B	Phase III – R, DB, DD, MC study	Alatrofloxacina 300 mg i.v. Trovafoxacin 200 mg	Impipenem/cilastatin 1 g/8 h i.v. Amocycillin/clavunatic acid 500/125 mg tid	<14	201/207/17–88 years	120	Intra-abdominal infection
10. Surgical prophylaxis							
10A	Phase III – R, DB, DD, MC study	Alatrofloxacina 200 mg i.v. single dose	Cefotexan 2 g i.v., single dose	NA	256/236/24–90 years	82	Elective colorectal surgery
10B	Phase III – R, DB, DD, MC study	Trovafoxacin 200 mg p.o. (single dose)	Cefoxitin 2 g i.v. (single dose or 2 doses)	NA	188/175/20–78 years	18	Elective abdominal or vaginal hysterectomy
11. Skin and soft tissue infections							
11A	Phase III – R, DB, MC study	Trovafoxacin 100 mg	Flucloxacillin 500 mg qid	7	140/135/16–92 years	37	Uncomplicated skin and soft DD, tissue infections
11B	Phase III – R, DB, MC study	Trovafoxacin 100 mg	Cefpodoxime proxetil 400 mg bid	7–10	221/225/16–88 years	32	Uncomplicated skin and soft DD, tissue infections
11C	Phase III – R, DB, DD, MC study	Alatrofloxacina 200 mg i.v. Trovafoxacin 200 mg	Piperacillin/tazobactam 3375 g i.v. Cefpodoxime proxetil 400 mg bid	10–14	144/142/18–90 years	36	Complicated skin and soft tissue infections
11D	Phase III – O, MC study	Trovafoxacin 200 mg	None	10–14	225/0/30–89 years	26	Foot ulcers and other infections
11E	Phase III – R, O study	200 mg trovafoxacin oral	Amoxicillin/clavulanate 500/125 mg tid	10–14	160/156/18–99 years	60	Complicated skin and soft tissue infections
12. Meningococcal meningitis in children							
12 A	Phase III – R, O study	Alatrofloxacina (3 mg kg ⁻¹ up to 200 mg od) i.v. or oral	Ceftriaxone (100 mg kg ⁻¹ od) i.v./i.m.	5	98/100/1–30 years	1	Epidemic meningococcal meningitis
Tolcapone							
BZ A	Phase II – DB, MC parallel-group study	Tolcapone 200 or 400 mg p.o. tid	Placebo Sinemet el. Madopar	9	64/33/66–68 years	6	Nonfluctuating parkinsonian patients
BZ B	Phase II – DB, MC parallel-group study	Tolcapone 50, 200 and 400 mg p.o. tid	Placebo Sinemet el. Madopar	6	112/42/62–63 years	12	Fluctuating parkinsonian patients
NZ C	Phase II – DB, MC parallel-group study	Tolcapone 50, 200 and 400 mg p.o. tid	Placebo Sinemet el. Levodopa	6	117/42/63–66 years	12	Fluctuating parkinsonian patients
NZ D	Phase III – DB, MC parallel-group study	Tolcapone 100 and 200 mg p.o. tid	Sinemet el. Levodopa	13 week efficacy, with an extension phase of further 9 months	136/66/63–65 years	12	Fluctuating parkinsonian patients

Table 2a

Continued

Study	Study design	Trovafoxacin/ alatrofloxacin	Comparator drug	Duration of treatment (days)	No. of treated/ comparator/age*	No. of centres	Included patients
NZ E	Phase III – DB, MC parallel-group study	Tolcapone 100 or 200 mg p.o. tid	Madopar	13 week efficacy, with an extension phase of further 9 months	119/58/62–64 years	24	Fluctuating parkinsonian patients
NZ F	Phase III – O, MC study	Tolcapone 200 mg p.o. tid	Bromocriptin 2.5/5 mg o.d.	8	72/74/61–65 years	19	Fluctuating parkinsonian patients
NZ G	Phase III – DB, MC parallel-group study	Tolcapone 100/200 mg p.o. tid	Placebo/Sinemet	26 week efficacy study with a secondary extension phase of further 65 weeks	196/102/63–67 years	20	Nonfluctuating parkinsonian patients
NN H	Phase III – DB, MC parallel-group study	Tolcapone 100/200 mg p.o. tid	Placebo/Sinemet	6	143/72/61–64 years	15	Fluctuating parkinsonian patients
NZ I	Phase III – O, uncontrolled, MC study	Tolcapone 200 mg p.o. tid	Madopar/Sinemet	12	484/–/63 years	44	Fluctuating and nonfluctuating patients
NZ J	Phase III – O, uncontrolled, MC study	Tolcapone 200 mg p.o. tid	Sinemet	12–18	139/–/65 years	13	Fluctuating parkinsonian patients
BZ K	Phase III – O, uncontrolled, MC study	Tolcapone 200 mg p.o. tid	Madopar/Sinemet	12	75/–/62 years	12	Fluctuating parkinsonian patients
BZ L	Phase III – O, uncontrolled, MC study	Tolcapone 200 mg po. tid	Madopar/Sinemet	12	26/–/64 years	6	Nonfluctuating patients
Rituximab							
R 1	Phase VII – O, uncontrolled, MC study	10–500 mg m ⁻² i.v. single dose	None	1 day	15/15/38–73 years	40	Relapsed, low, intermediate and high grade B-cell lymphoma
R 2	Phase II – O, uncontrolled, MC study	125–375 mg m ⁻² i.v. infusion once weekly	Historic controls in a single-agent treatment (cladribine/fludarabine)	4	47/47*29–81 years	40	Relapsed, low, intermediate and high-grade B-cell lymphoma
R 3	Phase II – O, uncontrolled, MC study	Multiple dose (375 mg m ⁻² i.v.) infusion once weekly (six doses administered on day 1, 6, 48, 90, 134, 141)	CHOP: cyclophosphamide, doxorubicin, vincristin, prednisone	21	40/40**29–77 years	40	Low-grade or follicular B-cell lymphoma
R 4	Phase III – O, uncontrolled, MC study	375 mg m ⁻² i.v. infusion once weekly	Historic controls in a single-agent treatment (cladribine/fludarabine)	4	166/166*22–79 years	40	Relapsed, low-grade or follicular B-cell lymphoma
R 5	Phase II – O, uncontrolled, MC study	375 mg m ⁻² i.v. infusion once weekly	None	8	32/20*35–74 years	40	Relapsed, low-grade or follicular B-cell lymphoma
R 6	Phase II – O, uncontrolled, MC study	375 mg m ⁻² i.v. infusion once weekly combined modality with IFN-alfa	None	4	35/3*31–79 years	40	Relapsed, low-grade or follicular B-cell lymphoma
R 7	Phase II – O, uncontrolled, MC study, ongoing	375 mg m ⁻² i.v. infusion once weekly	None	4	13/10*40–79 years	40	Low-grade or follicular B-cell lymphoma
R 8	Phase II – R, O, MC study, ongoing	375–500 mg m ⁻² once weekly	None	8	29/0*/not available	40	Low-grade or follicular B-cell lymphoma
R 9	Phase II – O, uncontrolled, MC study, ongoing	Multiple-dose (375 mg m ⁻² i.v.) once every 3 weeks	CHOP	18	9/0*/not available	40	Low-grade or follicular B-cell lymphoma

*Trovafoxacin/alatrofloxacin: total 5123 (oral) and 1513 (i.v.) patients. Tolcapone: total 1536 patients. Rituximab: total 282 patients. For Rituximab, the number of patients is calculated based on how many were calculated for safety and efficacy, respectively. The company study numbers have been encrypted into a code. The original numbers remain with the authors. R, Randomised; O, open; DB, double blind; DD, double dummy; NA, no information.

Table 2b

Overview of clinical Phase II and III trials in registration files (shorter version)

Phase II and III clinical trials				
Study	Study design	Dosage trovafloxacin/alatrofloxacin*	Treatment (days)	No. treated
Trovafloxacin				
1. Lower respiratory tract infections: community-acquired pneumonia				
1A – Phase II	R, DB, DD study	200 mg/300 mg od	10	102
1B + 1C – Phase III	R, DB, DD study	200 mg od	7–10	150
1D – Phase III	R, DB study	200 mg i.v. to 200 mg od	7–10	196
1E – Phase III	R, DB, DD study	200 mg i.v. to 200 mg od	7–10	111
2. Nosocomial pneumonia				
2A – Phase III	R, DB, DD study	300 mg i.v. to 200 mg od	10–14	127
2B – Phase III	R, O study	300 mg i.v. to 200 mg od	10–14	135
3. Acute exacerbations of chronic bronchitis (AECB)				
3A – Phase II	R, DB, DD study	100/300 mg od	10	148
3B – Phase III	R, DB, DD study	100/200 mg od	5	279
3C – Phase III	R, DB study	100 mg od	7	210
3D – Phase III	R, O study	100/200 mg od 3–7 days	5	279
3E – Phase III	R, DB study	100 mg od	7	131
4. Sinusitis				
4A – Phase III	O study	200 mg od	10	254
4B – Phase III	R, DB, DD study	200 mg od	10	203
4C – Phase III	R, O study	200 mg od	10	205
5. Urinary tract infections: acute, uncomplicated				
5A – Phase II	R, DB, DD study	100 mg od bid	7	146
5B – Phase III	R, DB study	100 mg od bid	3–7	364
6. Prostatitis				
6A – Phase III	R, DB, DD study	200 mg od	28	NA
7. Sexually transmitted diseases				
7 A + B – Phase II	R, O study	50, 100, 200 mg od	7	441
7C + D – Phase III	R, DB, DD study	100 mg/200 mg	5	800
8. Pelvic inflammatory disease				
8A – Phase III	R, DB, DD study	200 mg i.v. to 200 mg od	14	79
8B – Phase III	R, DB, DD study	200 mg od	14	149
9. Surgical and pelvic infections				
9A – Phase III	R, DB study	300 mg i.v. to 200 mg od	<14	160
9B – Phase III	R, DB, DD study	300 mg i.v. to 200 mg od	<14	201
10. Surgical prophylaxis				
10A – Phase III	R, DB, DD study	200 mg i.v.	NA	256
10B – Phase III	R, DB, DD study	200 mg	NA	188
11. Skin and soft tissue infections				
11A + B – Phase III	R, DB, DD study	100 mg od	7–10	361
11C – Phase III	R, DB, DD study	200 mg i.v. to 200 mg	10–14	144
11D – Phase III	O, MC study	200 mg od	10–14	225
11E – Phase III	R, O study	200 mg od	10–14	160
12. Meningococcal meningitis in children				
12A – Phase III	R, O study	3 mg kg ⁻¹ up to 200 mg od	5	98
Tolcapone				
Dosage tolcapone				
BZ A – Phase II	DB parallel-group study	200/400 mg tid	9	64
BZ B + C – Phase II	DB parallel-group study	50/200/400 mg tid	6	229
NZ D + E – Phase III	DB parallel-group study	100/200 mg tid	13 weeks	255
NZ F – Phase III	O study	200 mg tid	8	72
NZ G – Phase III	DB, parallel-group study	100/200 mg tid	26 weeks	196
NN H – Phase III	DB, parallel-group study	100/200 mg tid	6	143
NZ I – Phase III	O, uncontrolled study	200 mg tid	12	484
NZ J – Phase III	O, uncontrolled study	200 mg tid	12–18	139
BZ K + L – Phase III	O, uncontrolled study	200 mg tid	12	101

Table 2b

Continued

Rituximab		Dosage rituximab		
R 1 – Phase I/II	O, uncontrolled study	10–500 mg m ⁻² i.v.	1 day	15
R 2 – Phase II	O, uncontrolled study	125–375 mg m ⁻² i.v. once weekly	4	47†
R 3 – Phase II	O, uncontrolled study	375 mg m ⁻² i.v. once weekly	21	40†
R 4 – Phase III	O, uncontrolled study	375 mg m ⁻² i.v. once weekly	4	166†
R 5 – Phase II	O, uncontrolled study	375 mg m ⁻² i.v. once weekly	8	32†
R 6 + 7 – Phase II	O, uncontrolled, study	375 mg m ⁻² i.v. once weekly	4	48†
R 8 – Phase II	R, O study	375–500 mg m ⁻² once weekly	8	29†
R 9 – Phase II	O, uncontrolled study	375 mg m ⁻² i.v. once weekly	18	9†

*Trovafoxacin/alatrofoxacin: total 5123 (oral) and 1513 (i.v.) patients; tolcapone: total 1536 patients; rituximab: total 282 patients. †For rituximab, the number of patients is calculated based on how many were calculated for safety and efficacy, respectively. The company study numbers have been encrypted into a code. The original numbers remain with the authors. R, Randomised; O, open; DB, double blind; DD, double dummy; NA, no information.

Figure 1

Incidence (%) of reported adverse drug reactions (ADRs) for trovafoxacin/alatrofoxacin. General, (□); App./Inj./Incision/Insertion Site, (■); Gastrointestinal, (□); Skin/Appendages, (□); Central and peripheral nervous system, (■); Reproductive, (□); Respiratory, (■); Urinary system, (□)

adult subjects [13]. Figure 1 shows the incidence (>1%) of ADRs reported during the clinical trials distributed on system organ classes. During a treatment period of a maximum of 14 days, the rise in aspartate aminotransferase (AST) was reported as <1% and of alanine aminotransferase (ALT)=1%, and at the same level as comparator drugs. One clinical study (indication not claimed) with a prolonged treatment period of 28 days showed an ‘unacceptable’ rise, defined by the pharmaceutical company, in liver function disturbances (protocol no. 6A). One case of hepatocellular damage was in study no. 1B.

Tolcapone

Tolcapone was investigated in three Phase II and nine Phase III clinical trials, including 1536 adult subjects [14]. Figure 2 shows the incidence (>1%) of ADRs reported during the clinical trials. Elevated liver enzymes, ALT (serum glutamate pyruvate transaminase) or AST (serum

Figure 2

Incidence (%) of reported adverse drug reactions (ADRs) for tolcapone. Tolcapone 50 mg/78 patients, (□); Tolcapone 100 mg/296 patients, (■); Tolcapone 200 mg/1188 patients, (□); Tolcapone 400 mg/135 patients, (□)

glutamic-oxaloacetic transaminase), above 3× upper limit of normal (ULN) were detected in 1.7% and 3.1% of patients receiving tolcapone, 100 mg and 200 mg tid. Elevations of hepatic transaminases occurred in a dose-proportional manner, most frequently by the second to fourth months of treatment. However, there was some uncertainty about the temporal relationship to treatment, as the elevation was detected only at the last measurement for about one-third of patients and follow-up information is available for only 22 patients.

Two deaths were associated with dosage-related elevations of hepatic transaminases and frank jaundice, respectively, and isolated cases of neuroleptic malignant

syndrome complex were reported in studies conducted in Japan.

Rituximab

Rituximab has been investigated in eight Phase II and one Phase III clinical trials, including a total of 282 patients. Table 3 displays the incidence of ADRs reported during the trials. Three of the Phase II trials were ongoing at the time of approval, but safety data were included in the safety evaluations. Symptoms of cytokine release syndrome were reported in the clinical trials during infusions of the drug.

Assessment of SPC warnings

Hepatotoxicity Registration material for both trovafloxacin [13] and tolcapone [14] showed that the risk of hepatotoxicity was reported and detailed further in the SPC. Further investigation of the registration files showed that this information derived primarily from Phase I clinical trials and only to a limited extent from Phase II/III clinical trials, as patients with liver disease were excluded from them.

The SPC warned against the use of trovafloxacin in patients with severely impaired hepatic function (Child-Pugh C), as the drug has not been investigated for this patient group. Monitoring of liver enzymes is recommended for treatment with trovafloxacin exceeding 14 days.

For tolcapone the SPC recommended monitoring transaminases at treatment start and once a month thereafter for the first 6 months [14–15]. If a rise in transaminases occurred and treatment was continued, more frequent monitoring of complete liver function was recommended by the SPC. Treatment cessation was recommended if ALT exceeded 5× ULN or if clinical jaundice developed.

The SPC texts for tolcapone and trovafloxacin did not inform prescribers that some of the listed ADRs were less documented than others, e.g. liver toxicity, and consequently should require more attention from the prescribers if chosen for treatment of patients.

Tolcapone and neuroleptic malignant syndrome

Neuroleptic malignant syndrome was reported in the clinical trials with tolcapone and was thus already known at the time the drug was marketed. Information about ADRs was also provided in the SPC as a warning, but not accompanied by a recommendation on how to react upon observations of this character in patients, due to the severity of the ADR and despite the limited evidence at the time of marketing. Alternatively, the authorities might have demanded that the company set up further studies to investigate the prevalence of the neuroleptic malignant syndrome in relevant patients.

Rituximab and cytokine release syndrome Cytokine release syndrome [16] is a common, immediate complication occurring with the use of T-cell antibody infusions [17]

and other cancer drugs. Symptoms include fever, hypotension, pyrexia and rigors, which can lead to pulmonary oedema if the patient is fluid overloaded. Cytokine release syndrome were not mentioned directly in the SPC, even though it was known to occur with the infusion of cancer drugs [17] and mentioned in the assessor's report; however, all symptoms of the cytokine release syndrome are listed in the SPC.

Discussion

The main findings of this study are:

Registration material and the SPC contained observations/data on the analysed ADR cases, which have not been followed up with further clinical trials or other form of documentation.

The registration material contained limited data/information about the ADR profiles of the drugs in sub-populations, such as patients with liver and kidney disease. The analysed ADR data covered several areas of therapy with different requirements as to the documentation of efficacy and safety. Therefore, the basis for documentation in the registration material was very different for the different drugs, making the comparison of the various ADR cases difficult.

Creation of knowledge about ADRs

In the cases analysed, it was found that the reported ADR data were repeated in the SPC without any further processing, which means that they remained observations, i.e. information documented but not converted into new knowledge [12]. The observations on the explored ADR cases were fewer, but evaluated by the regulatory assessors as more serious than the most frequently reported ADRs in Phase II and III clinical trials. The practice of repeating isolated observations/data in the SPC text seems alarming. The character of the SPC text cannot be considered suitable as a basis for knowledge creation about ADRs for prescribers, as the text is simply a warning and does not invite further follow-up. Monitoring is thus relegated to the postmarketing period, primarily in the form of spontaneous reporting of ADRs, despite the fact that this process does not contribute the necessary knowledge [18] about ADRs, mainly because of underreporting and lack of significant evidence.

Limited knowledge about ADRs

Our findings support the supposition that knowledge about a drug's ADR profile is limited at the marketing stage due to limitations of the randomized clinical trials, e.g. the often relatively short treatment period under controlled conditions, as well as the selected patient populations used in the trials [19]. Detection of rare and unexpected

Table 3

Incidence (%) of reported ADRs for rituximab

Body system	Monotherapy %	Long-term follow-up %	Severe ADRs Monotherapy %	Long-term follow-up severe ADRs %
Fever	53.9	2.8		0.4
Chills	34.8		2.1	0.4
Nausea	23.4	1.8	0.7	
Asthenia	18.8	3.2	0.7	
Headache	17.7	1.4	1.1	0.7
Pruritus	14.5		0.4	
Pain	13.5	2.1	1.1	
Angioedema	12.8		0.4	
Rhinitis	12.1	1.4	0.4	
Rash	11.3	2.1	0.4	
Night sweats	11.0	2.8		0.4
Vomiting	11.0	1.1	0.4	
Bronchospasm	10.3		1.4	
Hypotension	10.3		0.7	
Abdominal pain	9.2	1.4	0.7	0.4
Thrombocytopenia	9.2	1.8	1.8	0.4
Leukopenia	8.9	5.3	2.1	1.4
Cough increase	8.5	1.8	0.4	
Diarrhoea	8.2	1.4	0.4	
Urticaria	7.8		1.1	
Myalgia	7.1			0.4
Arthralgia	7.4	2.1	0.4	0.4
Back pain	7.4		1.1	
Dizziness	7.1	1.1		0.4
Infection	7.1	4.6	0.4	0.4
Neutropenia	7.1	6.4	1.8	3.5
Sinusitis	5.7	2.8	0.4	
Flushing	5.3			
Chest pain	5.0			
Anemia	4.6		1.4	0.4
Hyperglycaemia	4.6	2.5	0.4	0.7
Hypertension	4.6		0.4	
Dyspnoea	4.3		0.7	
Peripheral oedema	4.3	2.5		
Herpes simplex	4.3		0.4	0.4
Lacrimation disorder	4.3			
Neck pain	3.5			
Anxiety	3.2			
Pharyngitis	3.2	1.1		
LDH increase	3.2	1.8		
Sweats	3.2	1.1	0.4	0.4
Dyspepsia	2.8	1.4		
Depression	2.8			
Paraesthesia	2.8			
Weight decrease	2.5	1.4		
Anorexia	2.5			
Oedema	2.5			
Hyperaesthesia	2.5			
Agitation	2.1			
Bradycardia	2.1			
Malaise	2.1			
Nervousness	2.1			
Facial oedema	2.1			
Insomnia	1.8			
Procedure site pain	1.8			
Urinary tract infection	1.4			
Pneumonia		1.8		0.4

Table 3

Continued

Body system	Monotherapy %	Long-term follow-up %	Severe ADRs Monotherapy %	Long-term follow-up severe ADRs %
Herpes zoster		1.1		0.4
Arrhythmia			0.7	
Asthma			0.7	
Spontaneous bone fracture			0.4	0.4
Skin carcinoma			0.4	
Coagulation disorder			0.4	
Creatinine PK increase			0.4	
Hypercalcaemia			0.4	
Hypertonia			0.4	
Anaemia aplastic				0.4
Bronchiolitis				0.4
Heart failure				0.7
Myocardial infarction				0.4
Kidney calculus				0.4
Axilla pain				0.4
Bone pain				0.4
Retinal disorder				0.4
Sepsis				0.4
Abnormal vision				0.4

ADRs in clinical trials is rare and frequently neglected in the assessment of new drugs [19].

The analysis of ADR cases also revealed very limited knowledge of the 'behaviour' of the drugs in special populations. The registration material showed that knowledge about the behaviour of trovafloxacin and tolcapon is very limited in patients with liver disease, because only Phase I clinical trials were conducted on patients with moderately reduced liver function, even though in practice these drugs will be used to treat patients with liver disease because of the lack of alternatives.

Considering the seriousness of the ADR reports about hepatotoxicity and the observations from clinical studies, the manufacturer should have been requested, prior to marketing of the drug, to conduct further clinical trials to clarify the extent of the risk of ADRs. The clinical trials used as the basis for reintroducing tolcapon on the market showed that there is no causal relationship between hepatotoxicity and the use of tolcapon in the reported ADR cases [16].

Rituximab's status as an orphan drug, which carries with it less stringent requirements for the number of Phase II/III clinical trials, also contributes to lowering the level of knowledge about ADRs at the marketing stage. In most cases, more numerous and more serious ADRs are tolerated for cancer drugs than for drugs in general. Therefore, it is difficult to evaluate the extent to which a stronger warning about ADRs could have prevented the ADR cases that occurred or simply resulted in an information overload of knowledge already available. It is unclear from the material why the rituximab SPC was accepted by the

authorities without directly mentioning cytokine release syndrome and without warnings about this condition, since this ADR is known to be serious, and hence usually monitored during treatment of cancer patients [17].

Better exposure of the ADR profile of drugs before they are marketed would necessitate more clinical trials of longer duration conducted on less selective patient populations than is the practice today. Obviously, such a change in practice would make it more difficult to obtain rapid approval of new cancer drugs or orphan drugs, or any drugs for that matter.

Instead, the authorities might give higher priority to following up on the rare and serious ADRs that are reported during drug development, and set more stringent requirements for drug manufacturers about conducting supplementary trials on specific safety issues and patient populations.

Furthermore, the quality of the SPCs could be improved, e.g. by setting out more stringent and more precise recommendations for the prescribers, so that they would have better guidelines to follow. Because of experiences with the recurring cases of serious and unexpected ADRs, which emerge after marketing of the drugs, the regulatory authorities have found it necessary to tighten up the regulatory demands in the licensing process regarding safety issues. Both the American and European regulatory authorities have set in motion a new tool, Risk Management plans [1], in order to react faster to new potential safety issues after marketing. The plans include the monitoring of safety data of a serious character reported during the clinical trials, but not considered

important enough to be further investigated before marketing of the drugs.

Strengths and weaknesses of the study

This is the first qualitative, empirical study to evaluate retrospectively selected ADR scenarios based on information about ADRs reported during Phase II and III clinical trials in order to evaluate the extent to which current knowledge about ADRs was available before the marketing authorization of the drugs. The choice of other ADR scenarios for analysis could have given a different result with regard to the types and extent of ADRs. It may also be possible that information in other drug cases has been taken into account and hence prevented further safety problems.

Conclusions

Knowledge creation about ADRs is important both before and after the marketing stage, because only limited knowledge about the ADR profile of the drugs is produced during drug development.

The information on ADRs reported during drug development does not automatically become new knowledge, but rather remains unprocessed in the form of observations in SPC, and thus does not necessarily initiate a knowledge-creation process.

More systematic and active follow-up on reports of serious ADRs in Phase II/III clinical trials would contribute more knowledge about the ADR profile and thus prevent more problems with unexpected and serious ADRs. If drug manufacturers undertook a more active and effective marketing of SPC data, results would probably contribute to more knowledge creation about ADRs. That would be in the best interests not only of patients, but also of manufacturers, as drug recalls are an expensive waste of their resources and may threaten their image.

REFERENCES

- 1 Dukes MNG. The Laws and Ethics of the Pharmaceutical Industry, 1st edn. Amsterdam: Elsevier, 2006.
- 2 SoRelle R. Withdrawal of Posicor from market. *Circulation*. 1998; 98: 831–2.
- 3 EMEA. Sertindole <http://www.emea.eu.int/pdfs/human/referral/Sertindole/285202en.pdf> (last accessed: 13 October 2006)
- 4 Horton R. Vioxx, the implosion of Merck, and the after shocks at the FDA. *Lancet* 2004; 364: 1995–6.
- 5 Loke Y, Price D, Derry S, Aronson JK. Case reports of suspected adverse drug reactions – systematic literature survey of follow-up. *BMJ* 2006; 332: 335–9.
- 6 Aronson JK, Hauben M. Anecdotes that provide definitive evidence. *BMJ* 2006; 333: 1267–9.
- 7 CHMP's Assessment Report on the Suspension of Trovan. EMEA/H/C/158/00/0/0/ (internal document).
- 8 CHMP's Assessment Report on Suspension of Alatrofloxacin. EMEA/H/C/160/00/0/0/ (internal document).
- 9 CHMP's Assessment Report on the Suspension of Tolcapon. EU/1/97/044/001–006 (internal document).
- 10 CHMP's Assessment Report on the Evaluation of MabThera. EMEA/40532/98 (internal document).
- 11 Strom BL. *Pharmacoepidemiology*. Chichester: John Wiley, 2005.
- 12 Nonaka I, Takeuchi H. *The Knowledge Creating Company*. Oxford: University Press, 1995.
- 13 Rapporteurs' Assessment Report of the Dossier of Trovan. EMEA/H/C/158/159/160/161 (internal document).
- 14 Rapporteurs' Assessment Report of the Dossier of Tasmar. EMEA/H/C/131/00–01/0/0 (internal document).
- 15 Rapporteurs' Assessment Report of the Dossier of MabThera. EMEA/H/C/165/01/01 (internal document).
- 16 EMEA. EPARs for authorised medicinal products for human use. <http://www.emea.europa.eu/humandocs/Humans/EPAR/tasmar/tasmar.htm> (last accessed: 13 October 2006)
- 17 Hank JA, Albertini M, Wesly OH, Schiller JH, Borchert A, Moore K, Bechhofer R, Storer B, Gan J, Gambacorti C. Clinical and immunological effects of treatment with murine anti-CD3 monoclonal antibody along with interleukin 2 in patients with cancer. *Clin Cancer Res* 1995; 1: 481–91.
- 18 Aagaard L, Soendergaard B, Andersen E, Kampmann JP, Hansen EH. Creating knowledge about adverse drug reactions: a critical analysis of the Danish reporting system from 1968 to 2005. *Soc Sci Med* 2007; Jun 11; [Epub ahead of print].
- 19 Hansen EH. Technology assessment in a user perspective – experiences with drug technology. *Int J Technol Assess Health Care* 1992; 8: 150–65.