Drug Safety 2005; 28 (11): 971-980
0114-5916/05/0011-0971/$34.95/0

Risk Management Strategies in the Postmarketing Period

Safety Experience with the US and European Bosentan Surveillance Programmes

Eleanor S. Segal, Cecile Valette, Laurence Oster, Luc Bouley, Catarina Edfjall, Peter Herrmann, Massimo Raineri, Mary Kempff, Saundra Beacham and *Cinda van Lierop*

Departments of Global Drug Safety, Drug Regulatory Affairs and Biometry, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland

Abstract

In view of the shortcomings of the current system for postmarketing drug surveillance that is based on voluntary spontaneous adverse drug reaction (ADR) reporting, new approaches are needed.

We describe an approach involving a combination of limited distribution, patient and physician education, as well as a novel pharmacovigilance system that is capable of promoting the safe and adequate use of a new drug. Importantly, it provides the possibility of calculating true ADR occurrence rates, as the exposed population (denominator) and the number of patients with events (numerator) are known. These measures were taken for the oral dual endothelin ET_A/ET_B antagonist bosentan (Tracleer®). In recent guidelines issued by the European Society of Cardiology, American College of Chest Physicians and the WHO, this drug is considered as first-line oral treatment for the treatment of pulmonary arterial hypertension, a devastating orphan disease associated with a poor prognosis. Bosentan was approved in 2001/2 on the basis of two pivotal studies that showed improved exercise capacity and haemodynamic parameters while delaying time to clinical worsening. Elevations in serum liver aminotransferase levels of >3 times the upper limit of normal were noted in 10.2% of patients (placebo-subtracted incidence). Therefore, liver function tests have to be performed on a regular basis. In addition, bosentan has potential as a teratogen.

In the US, a controlled distribution network for bosentan (Tracleer® Access Program [T.A.P.]) and the development of a patient database to follow patients was set up. Accompanied by comprehensive physician and patient education programmes, T.A.P. was developed to provide a mechanism to assist with the primary risk management goals for bosentan therapy, namely pregnancy prevention and liver enzyme monitoring and prevention of hepatic injury.

In Europe, the Tracleer® Excellence (TRAX PMS) database is a novel European non-interventional, prospective, internet-based surveillance system initiated by the manufacturer in cooperation with the European Medicines Agency. It collected potential safety signals associated with bosentan use including adverse events, elevations of liver aminotransferase levels, other abnormal laboratory values, death and hospitalisation. TRAX PMS has accrued 79% of all known patients in

the EU and the data provide supportive 'real-life' evidence on the long-term safety of bosentan.

The two different systems had similar goals and outcomes. The data received concerning thousands of patient-years of use have confirmed the clinical trial results regarding product safety and the favourable benefit/risk ratio of bosentan, especially with regard to known type A adverse events. The clinical monitoring algorithm has also been confirmed. In addition, no rare type B events were uncovered despite the increased reporting rate. These systems might serve as templates for future pharmacovigilance efforts regarding drugs that require particular safety attention.

The spontaneous reporting of adverse drug reactions (ADRs) has been the mainstay of pharmacovigilance worldwide for many decades and is the principal method of identifying ADRs. However, in a recent series of publications the substantial shortcomings of the current postmarketing drug surveillance system in the US, which is basically the same in the EU, were highlighted.[1,2] The identification of possible ADRs, which relies on spontaneous reporting to the manufacturer or regulatory authorities, is viewed as "fundamentally a 1950s-era approach".[1,3] The passive collection of spontaneous reports leads to poor, incomplete and biased reports. Vast under-reporting is the rule, as approximately only 1–10% of possible ADR reports are collected.[4,5] Thus, the present system certainly does not live up to the expectation that ADRs for new drugs are identified early in order to limit exposure of the public to the potential hazards of drugs.

However, there are novel approaches to pharmacovigilance available that are capable of tackling the issue of under-reporting and providing both accurate numbers of events (numerators) and accurate numbers of the exposed individuals (denominators). Both are needed to calculate true ADR rates,[1,6] which can then be used to continually evaluate the benefit/risk profile of a drug.

We present two examples of innovative surveillance systems that accompanied the launch of a new drug, bosentan (Tracleer® [1]). Both systems were part of a comprehensive programme that comprised control of drug distribution, patient and physician education and pharmacovigilance measures.

1. Potential Liver Liability and Teratogenicity of Bosentan

Bosentan, an oral dual endothelin ET_A/ET_B receptor antagonist, was approved in 2001/2 with an orphan drug status in the US and the EU for the treatment of pulmonary arterial hypertension (PAH), a rare, devastating disease involving endothelin that has a poor prognosis.[7,8] Although the drug today is considered a first-line therapy for PAH,[9,10] at the time of approval clinical data were limited. It was suggested that PAH is encountered so rarely that it would not be possible to collect comprehensive data on clinical safety. Indeed, the total bosentan patient exposure at the time of submission was only 59 patient years, which is marginal compared with the thousands of patient-years that are usually reported in dossiers of cardiovascular drugs. In terms of safety, in the pivotal BREATHE (Bosentan Randomized trial of Endothelin receptor Antagonist THErapy)-1 study the number and nature of adverse events (AEs) were similar between bosentan and placebo, with the exception of flushing, oedema/leg oedema, nasopharyngitis and especially abnormal hepatic function, which were all more frequent in patients receiving bosentan.[11] In a pooled safety analysis of eight placebo-controlled clinical trials (two of which were for the indication of PAH including BREATHE-1), bosentan, at dosages of up to 2000 mg/day, was found to be associated with an increase in liver aminotransferase levels (ALT and/or AST) of >3 times the upper limit of normal (ULN) in an average of 11.2% of patients versus 1.8% of patients receiving placebo.[11,12] Aminotransferase level elevations developed over

1 The use of trade names is for product identification purposes only and does not imply endorsement.

several weeks, occurred primarily in the first 4–6 months of treatment, were dose related and reversible without sequelae either during continued treatment with bosentan (approximately half of the cases) or upon discontinuation of bosentan. In addition, preclinical data had shown that bosentan has a potential for teratogenicity.[13,14]

To address these potential safety issues, access to the drug was limited both in the US and in Europe and guidelines for physicians were detailed in the product information stipulating regular monitoring of liver enzyme levels. Aminotransferase levels were to be measured at baseline and subsequently every month, or 2 weeks after dose increase. In addition, recommendations for use of more than one form of birth control and regular pregnancy monitoring for female patients of childbearing age were included in the US package insert and summary of product characteristics (SPC).

In the context of postapproval commitments, the marketing authorisation holder (MAH) of bosentan has instituted systems for physician registration of patients, reminders to physicians for monthly liver enzyme testing in the EU and monthly patient reminders in the US.

To validate that these treatment algorithms were adequate under clinical practice conditions to decrease the risk of occurrence of severe liver injury, two separate systems were set up in cooperation with the US FDA and the European Medicines Agency (EMEA), both sharing the same purpose: to promote the safe use of bosentan. Table I provides an overview of both systems, the Tracleer® Access Program (T.A.P.) in the US and the Tracleer® Excellence (TRAX PMS) system in Europe.

2. Tracleer® Access Program in the US

2.1 Description

In the US, bosentan is only available through the T.A.P., a controlled distribution system. Only a few speciality distributors have been licenced to distribute the drug. The principal features of T.A.P. are summarised in table II. Importantly, both physicians prescribing bosentan and patients receiving the drug have to be registered, using a form that is duly signed as a consent to release information to Actelion and the distributor. Before an individual patient can be prescribed bosentan, this written certification must be provided by the practitioner stating that: (i) bosentan is being prescribed for a medically appropriate use in the treatment of PAH, as described in the full prescribing information; and (ii) the physi-

Table I. Postapproval commitments in the US and EU

Type	US	EU
Postmarketing surveillance	No	Yes, TRAX PMS system
Controlled distribution	Yes, T.A.P.	Yes
Medical information	Yes, medication guide, USPI	Yes, patient reminder card, prescriber kit, SPC
Regular reporting	Yes, annually	Yes, semiannually
Safety reporting	Yes, USPR[a] (courtesy PSUR)	Yes, PSUR[b] (courtesy USPR)
Annual review of fulfilling commitment	Yes	Yes
Patient identity known by system	Yes	No
Patient demographics	Yes	Yes (partial)
Prescriber details	Yes	Yes, if legally possible
Information on bosentan discontinuation[c]	Yes	Yes
Capture of AEs relating to the liver	No	Yes
Capture of AEs relating to pregnancy	No	Yes
Reminder about liver function tests	Yes, to patient	Yes, to prescriber

a Reported quarterly × 12 quarters, then annually (waiver received from the US FDA to provide USPRs annually after 12 quarterly reports submitted).

b Reported semiannually.

c When bosentan is discontinued, no survival status is captured thereafter unless spontaneously reported by the prescriber to the Actelion Global Drug Safety (GDS) department.

AEs = adverse events; **PSUR** = Periodic Safety Update Report; **SPC** = summary of product characteristics; **T.A.P.** = Tracleer® Access Program; **TRAX PMS** = Tracleer® Excellence; **USPI** = US package insert; **USPR** = US Periodic Report

Table II. Features of the Tracleer® Access Program in the US

1. Complete registration of all patients receiving Tracleer®
2. Complete registration of practitioners who prescribe Tracleer®
3. Distribution of Tracleer® through a controlled specialty distribution network
4. Distribution of the medication guide to patients with each shipment of Tracleer®
5. Initial distribution of Tracleer® is to occur only after receipt of appropriate prescribing form by the distributor
6. Patient reminder monthly regarding liver and pregnancy tests
7. Notification of discontinuation of patient to prescriber; collection of data relating to liver function, pregnancy or related adverse event or death

cian has reviewed the liver and pregnancy warnings with the patient and has committed to undertaking the appropriate monitoring of liver function tests and testing for pregnancy (if the patient is a female of child-bearing potential). This represents an important element of physician education.

An integral component of the T.A.P. is the telephone call by the speciality distributor each month to each individual patient prior to dispatching the next month's supply of bosentan. The purpose of the call is to determine whether the patient has had a liver function test and (if appropriate) a pregnancy test each month. In the event that the patient is unsure of whether the test was done, the distributor is required to remind the patient's physician of the need to conduct such tests. Thus, the compliance of patients is closely followed up and physicians are notified immediately about patients not compliant with the liver function test and pregnancy monitoring requirements. The percentage of calls requiring physician notification has been 3–7% (mostly due to patients neglecting to obtain the needed blood work), suggesting that the patient population can be well educated regarding risk management. At the time of the monthly call from the specialty distributors, if the patient did not wish to continue bosentan or if the patient had died, the patient's physician was called to see if the reason for discontinuation was medical, in which case the Actelion Global Drug Safety (GDS) department would follow up. In those cases, liver function test abnormalities causing discontinuation of bosentan would be reported. The TRAX PMS system showed that nearly 50% of patients with abnormal liver function tests can continue or return to bosentan following resolution. However, as most LFT abnormalities in the US are collected as part of discontinuation data from T.A.P., a number of patients in the US who experience a transient increase in liver enzyme levels that does not require discontinuation are not spontaneously reported. Pregnancies have been spontaneously reported and/or captured at the time of discontinuation. As pregnancy itself is a life-threatening event for patients with PAH, most patients have elected to undergo therapeutic termination.

The outcomes of this surveillance in terms of liver function test monitoring and fetal exposure to the drug are summarised by the sponsor and reported regularly to the FDA. Expedited reports (within a 15-day period) are issued by the sponsor to the FDA in case of any pregnancy, any elevation in aminotransferase levels of $>8 \times$ ULN, any elevations of aminotransferase levels accompanied by an elevation of bilirubin level of $\geq 2 \times$ ULN or any clinical liver injury associated with hospitalisation, liver transplantation or death.

2.2 Challenges

The T.A.P. presents substantial challenges. It is apparent that the reminder systems for liver function and pregnancy testing are operating as planned; however, there are negative effects of these processes. First, the system is extremely labour intensive and costly. Second, the intensity of active query follow-up irritates physicians and is sometimes perceived as 'overdoing it'. Third, intensive training of distributors to understand reporting requirements is necessary (e.g. understand that death is a serious AE). Fourth, a large number of events are actually being solicited, including the majority of deaths occurring in the US following the use of bosentan for the life-threatening disease PAH. This means that most of the deaths followed up by the Actelion GDS department are considered by prescribers not to be drug related, but rather the consequence of normal disease progression in patients who, if untreated, have 50% mortality in 2.8 years from diagnosis.[15] A recent publication that followed patients from the two pivotal trials reported that approximately 85% of patients with primary pulmonary hypertension (idiopathic PAH) who had participated in the trials were still alive after 3 years.[16] The number of deaths reported in the T.A.P. followed a similar pattern, with a comparable percentage of

deaths after 3 years (15.5%).[17] Thus, the follow-up of every death occurring in the first 2 years of marketing authorisation, although confirming the predicted 'effectiveness' of bosentan, has not improved pharmacovigilance and has filled the safety database with unrelated AEs ('noise'). In order to resolve this AE over-reporting and to effectively separate true signals from noise, the following algorithm was approved by the FDA at the end of 2004. The healthcare provider/prescriber of all patients who discontinue bosentan will be actively questioned to determine whether the reason for the discontinuation was because of the drug (related death or any related AE) or if it had to do with liver or pregnancy reasons (even if considered unrelated by the prescriber). Related cases of death and AEs and any liver or pregnancy case will be entered into the MAH's safety database and followed up with both active and inactive queries (the latter meaning queries by mail without active probing of non-responders). So far, all reports of death from the T.A.P. have been entered into the safety database of the company. However, in future, unrelated cases of discontinuation due to death or AEs will appear in specialty distribution listings as 'death' or 'adverse event' but will not be entered into the safety database. Even so, these line listings will be continuously analysed by Actelion to ensure that there is no sudden increase in discontinuation due to death or AEs (if so, they can be further investigated on an individual basis and added to the safety database) and will be provided to all health authorities as aggregated data line listings in all periodic safety update reports.

3. Tracleer® Excellence (TRAX PMS) System in the EU

In the commercially launched EU countries, distribution of bosentan is as limited as it is in the US. The main point of the controlled distribution system in the various EU countries was to ensure that physicians could not prescribe bosentan unless they were appropriately educated regarding the risks. These physicians were also encouraged to participate in TRAX PMS. Each country had a different way of managing the system, according to local regulations. All bosentan prescribers who had been identified through a tailored distribution system (approved separately by each country) were contacted and provided with a prescriber kit containing information about TRAX PMS. Patient information is presently gathered from a total of 18 EU countries.

3.1 Description

TRAX PMS is a European non-interventional, prospective, internet-based postmarketing surveillance database. To our knowledge, it is the first real-time, bidirectional system serving pharmacovigilance purposes. The prespecified aims of the system were: (i) to ensure that the prescribing physicians were aware of the safety-related information (education); (ii) to supplement under-reporting of spontaneous AEs from prescribers by soliciting reports through a series of prompts by the system on a monthly basis for liver function test 'potential signals' and quarterly for other potential safety signals; and (iii) to provide regular and timely comprehensive postmarketing experience reports to the regulatory agencies.

Bosentan prescribers participate on a voluntary basis. Once registered as TRAX PMS users, they are requested to enter patient data into the system on a regular basis. This information is directly transferred via a secure internet connection from the prescriber to a central database. Aggregated data are reviewed weekly by the MAH's GDS unit to determine whether potential safety signals are present. The process is displayed in figure 1.

Data that were obtained included demographics, aetiology of PAH, New York Heart Association functional class at baseline and use of specific PAH medications. More than 95% of patients had more than one instance of data entry. Potential signals collected in TRAX PMS are grouped in two categories: safety related or non-safety related. *Potential safety signals* are: death, hospitalisation, pregnancy, serious AEs/ADRs, ADRs not listed in the SPC, liver test abnormalities, other abnormal laboratory values, transplantation, atrial septostomy or initiation of intravenous prostacyclin. It should be noted that the term 'potential safety signal' has been introduced in retrospect, when it was realised that none of the events recorded (e.g. medical reasons for discontinuation) became a true signal because none appreciably differed from the known safety profile of bosentan. *Non-safety signals* are: reasons for dis-

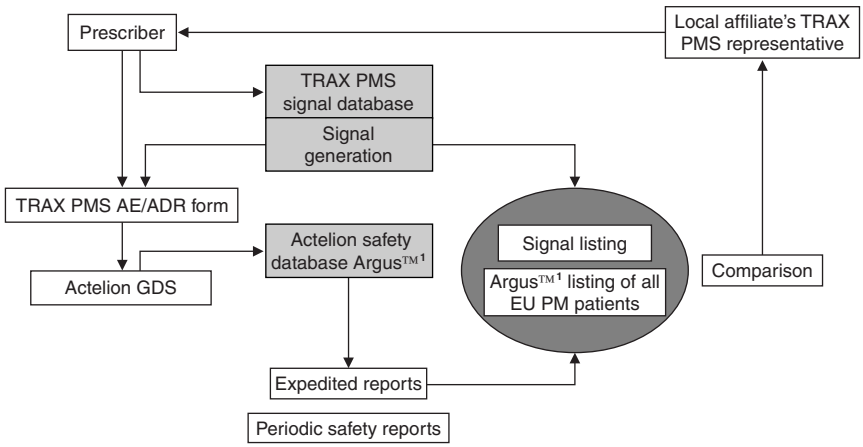

Fig. 1. Data reconciliation process between the Tracleer® Excellence (TRAX PMS) and Actelion Global Drug Safety (GDS) database. **1** Argus™ = Enterprise database from Relsys International Inc., Irvine, CA, USA. **ADR** = adverse drug reaction; **AE** = adverse event; **PM** = postmarketing.

continuation such as patient request, loss to follow-up or non-medical reasons.

Notifications are automatically provided in real time to the person entering information as to whether the MAH requires further information on the case. Importantly, mechanisms are built into the TRAX PMS to ensure those data that are classified as potential safety signals (but not the non-safety signals) result in the prompting of the prescriber to complete an AE/ADR form that is to be forwarded to the GDS department to enter into the safety database (Argus™). If a serious AE/ADR form is not completed despite persistent follow-up attempts, minimal information from the 'potential safety signal' in TRAX PMS is entered into the safety database without an official form. This allows the entry of potential signals into the safety database to remain at approximately 95%.

3.2 Causality Assessment and Expedited Reporting

In the patients not enrolled in TRAX PMS in the EU, the reporting rate was approximately 10%, whereas for TRAX PMS patients it was 30%.[18] As for the assessment of causality, the prescriber categorisation is accepted by the MAH, except in cases where the MAH will upgrade a case from 'unrelated' to 'related'. For example, almost all liver function abnormalities are upgraded to 'related' for the purposes of reporting, even when there may be a perfectly acceptable other cause (e.g. a patient with high alkaline phosphatase levels who underwent cholecystectomy for cholelithiasis and successfully continued bosentan).

Of note, because spontaneously reported 'events' are always considered 'reactions' for the purpose of reporting to health authorities, and are so defined in the safety database, these cases are recorded as related. When reviewing TRAX PMS data in the safety database, 47% of reported cases were considered related; about one-third of those were due to liver function abnormalities, which were almost considered related. This relationship more truly matches the 'real' relationship of reported events to the use of bosentan.

Expedited reporting is done for all related cases following the International Conference on Harmonisation and FDA guidelines for postmarketing surveillance and adhering to stricter special postmarketing reporting requirements for the liver function abnormalities that were imposed by the FDA at the time of approval. However, the configuration of Argus™ takes the most conservative approach to reporting. If any event in a case is serious, any event is unlabelled, or any event is related, the case-level assessment for purposes of expedited reporting will be serious, unlabelled and related (and, therefore, expeditable). This means that a case containing a related labelled event paired with an unlabelled but

unrelated event could result in an expedited submission to health authorities and ensures that any potential problem will be quickly identified.

3.3 Privacy Issues

To comply with data protection regulations, patients are assigned random numbers on the web database and the prescriber information is kept on a separate database. Thus, patients are identifiable to the GDS department as TRAX PMS patients only by the patient number noted on the AE/ADR form. The ADR forms that pop up on the screen for prescribers to fill out are not saved in the system or transmitted electronically, but must be printed out by prescribers and faxed to the safety department. Cross referencing of potential safety signals by GDS between the ADR forms received and TRAX PMS listings is done only with the unique TRAX PMS patient number and year of birth, since neither patient initials nor full date of birth are collected in the TRAX PMS system. When no form has been received, prescribers are contacted to ask them to fill out a form for the anonymous patient that they had entered into TRAX PMS, who is identified by the patient TRAX PMS number. Thus, only the physicians can match TRAX PMS numbers to their own patients. As patient privacy is protected and no additional diagnostic or monitoring procedures outside of the SPC are stipulated, no ethics committee approval or informed consent by individual patients is needed for TRAX PMS in most countries.

3.4 Reporting to Authorities, Prescribers and Pulmonary Arterial Hypertension Expert Panel

The status of the TRAX PMS programme implementation and enrolment, the safety signals detected in the system and the reasons for patient discontinuation are reported semiannually to the EMEA Committee for Medicinal Products for Human Use (CHMP). Participating physicians are informed on a regular basis about the amount of patient safety experience captured in the system and selected patient characteristics, as well as additional patient-specific information that they can retrieve regarding their own patients. In addition, a PAH expert board reviews the appropriateness of patient classification (when free text is input in the 'other' category of aetiologies of PAH, etc.) and safety data of the TRAX PMS and provides analysis and recommendations to the manufacturer. Participating physicians are regularly informed via newsletters. Congress presentations and scientific publications are authored by the PAH expert board.

3.5 Review of Liver Disorders by International Liver Safety Board

By convention, the use of the term 'liver function test abnormality' refers to increases in the serum levels of ALT and/or AST, and not to isolated bilirubin or alkaline phosphatase level elevations. For each patient, the most severe instance of liver function test elevation is reported by this convention.

Liver disorders are regularly reviewed on a case-by-case basis by a chartered International Liver Safety Board (ILSB) of experts established by the manufacturer, particularly with respect to a regulatory authority's requirements to pay particular attention to patients who had systemic symptoms attributable to liver injury. This included patients with malaise, fever and nausea, and patients who were jaundiced (total bilirubin level $>3 \times$ ULN) with little change in serum alkaline phosphatase levels ($<2 \times$ ULN) associated with mild elevations of aminotransferase levels ($>3 \times$ ULN). Patients meeting the criteria described above, due to any drug treatment, are considered to be patients at a 10% risk of fatal liver injury, as described by Zimmerman[19,20] and quoted in the FDA Working Group 'Clinical White Paper' on drug-induced liver injury.[21]

The small number of patients identified with liver injury meeting these criteria were carefully analysed by the manufacturer and the ILSB, along with all the rest of the patients who had potential liver signals, in order to evaluate the possible relationship to bosentan treatment and to determine whether a labelling change was indicated. So far, no change has been required. None of the patients specially identified as meeting the Zimmerman[19,20] criteria had fatal liver failure due to use of bosentan. This external ILSB review represents an important extra step in active pharmacovigilance.

3.6 Challenges

The Internet-based TRAX PMS system had to be reconciled with the MAH's drug safety database on a weekly basis. It became evident that physicians do not always fill out the online serious AE/ADR form, which necessitated additional efforts to retrieve the requested safety information. This ultimately required development of an entirely separate in-house tracking system to maintain records of additional enquiries undertaken when a potential safety signal was entered into TRAX PMS, but no serious AE/ADR form was received.

A challenge to both systems is the start of the clock for expedited reporting, as several possibilities for defining this time-point exist: (a) the date when the physician enters the safety signals in the system; (b) the date when this information is downloaded and reconciled; or (c) the date the faxed ADR form arrives at the manufacturer's GDS department. Another key question concerns the situation where safety signals have been received on 'hospitalisations' or 'adverse events', but the AE/ADR form has never been forwarded to the GDS. When would the clock start then? Would 'hospitalisation' be a serious AE? Would it be labelled or unlabelled? What about a report simply of an 'adverse event' or 'serious adverse event'? The MAH-devised complete tracking system was developed to follow up with reporting physicians when no AE/ADR form was received. However, if no response was obtained after several active and passive query attempts, undefined serious AEs and hospitalisations were considered not to meet the fourth criterion that defines a reportable case, the nature of a specific event; a patient, a drug and a reporter being the three other known criteria. Therefore, such cases were not entered into Argus™. As it was recognised that the TRAX PMS system provides three times as many AE reports as spontaneous reporting, the lack of entry of these few cases (<5% of potential signals did not get followed up with an appropriate AE/ADR form) was considered acceptable by the MAH and the FDA in a postmarketing inspection. The Establishment Inspection Report of an FDA inspection of postmarketing adverse drug event reporting practices at Actelion Headquarters in Allschwil, Switzerland in March 2004 was received with 'no action indicated', which represents the best possible outcome.

3.7 Current Status of TRAX PMS

Two and a half years after implementation of the system, it has fully lived up to the original expectations. The proportion of patients enrolled in TRAX PMS could be determined from the distributors in the various countries who had listings of the numbers of bottles of drugs supplied monthly for patients of various prescribers. According to these data, 79% of all bosentan-treated patients in the EU have been included in TRAX PMS. Extensive clinical experience data from both expert and non-expert prescribers are represented. Experience gained with >3500 patient-years of bosentan use between May 2002 and November 2004 in the EU indicates that signals generated under real-life conditions are consistent with the findings from clinical data, both in frequency and severity, particularly regarding adverse liver events (specifically, the overall occurrence of potential liver signals in TRAX PMS was 7.7%[18]). This confirms the original labelling recommendations. After the prescribed 2-year surveillance period was complete, the EMEA agreed to discontinue the programme because of confidence in the reliability of the known safety profile of bosentan.

4. Discussion

Following the launch of bosentan, it was necessary to capture, with the use of postmarketing surveillance, any change in the known frequency and severity of the liver enzyme level elevations reported in clinical trials (known type A reactions) in order to minimise risk to patients. However, the high reporting rate gives some assurance that rare type B reactions might also be noted and reported more quickly. As previous programmes such as the clozapine 'blood-for-drug' approach (in the first years after the 1989 approval patients had to have the results of their blood work reported prior to receiving their next prescription of clozapine) were considered unnecessarily restrictive, T.A.P. and TRAX PMS were developed with the input and cooperation of their respective health authorities.

What are the outcomes of the risk management strategy of using these programmes? Both systems offer substantial improvement compared with conventional spontaneous reporting. The existing enterprise safety database systems in place, such as Argus™, have the ability to produce answers to questions regarding demographics, frequency and seriousness of event occurrence and relationship to drugs, based either on the reporter's judgement or sponsor's opinion. The events can be analysed via tabulations and high-quality reports with line listings that can be produced and adapted to different types of internal and external queries.

Three times as many AEs have been reported in TRAX PMS as have been received from spontaneous reporting, and nearly 60 times as many patient years of exposure were collected in the postmarketing period in TRAX PMS alone compared with the pivotal trials (59 patient-years). The TRAX PMS programme has helped to determine a true postmarketing event rate (instead of just a reporting rate), since actual number of events as well as the number of exposed patients are known. Knowing the true numerator and denominator of events and patients has allowed the MAH to determine the percentage of events actually occurring in the postmarketing period, which cannot occur with spontaneous ADR reporting. TRAX PMS has been able to establish the safety profile of an orphan drug as it is used in the 'real world' of everyday practice.

Overall, the EU TRAX PMS system, which has functioned as a large simple safety survey, and the US controlled distribution system T.A.P. have both ensured that patients are appropriately monitored as described in the EU SPC and the US package insert. Keeping the limitations in mind (no 100% coverage of all patients, causality assessment by the prescriber), the quality and quantity of data and its early receipt provide support for current labelling or would represent a quick way to identify label changes, if needed. Spontaneous reporting could not allow such rapid analysis and response time, although it is still effective for the capture of rare, idiosyncratic (type B) events. Although it cannot be entirely excluded that type B events go unnoticed in TRAX PMS (as in other pharmacovigilance systems), it is more unlikely than in conventional systems since the vast majority of prescribers have participated in the system and reports were actively solicited at regular time intervals, including prompting for unexpected ADRs. Common non-serious AEs were not captured in TRAX PMS and therefore an increased frequency of occurrence of such events (e.g. 'nausea') would not have been reported. However, as a corollary of liver dysfunction, nausea was certainly captured. In fact, 'nausea', a frequently occurring event in the pivotal clinical trials, was added to the SPC as an event 'commonly' reported in the postmarketing period.

5. Conclusions

Although the systems in the US and the EU were run differently, they have similar goals and outcomes. They both have confirmed the clinical trial results regarding product safety and the benefit/risk ratio of bosentan, especially with regard to type A ADRs, by demonstrating no increased frequency or severity of such known reactions. A novel pharmacovigilance system such as TRAX PMS is clearly capable of identifying potential safety issues in the postmarketing period and may provide invaluable data to determine whether algorithms of prevention and treatment are sufficient. In the case of the present TRAX PMS system, it was determined that such algorithms were indeed sufficient to maintain the established benefit/risk ratio of bosentan and the programme was terminated by the CHMP, having fulfilled the manufacturer's postmarketing commitment regarding postmarketing surveillance. Although both systems are costly, labour intensive and provide challenges that needed to be overcome regarding patient privacy, data reconciliation and other issues, they can serve as templates for future pharmacovigilance efforts, particularly for drugs for which the orphan character of the treated disease only allows limited data collection prior to approval and drugs that require particular safety attention in the postmarketing period.

Similar systems might well be used for drugs in other classes and could complement any new health authority programmes implemented to oversee drug safety after a drug is marketed. However, a system of this kind is only acceptable for prescribers if the new product offers substantial benefits in terms of efficacy, cost or convenience and where the true

occurrence rate of significant AEs may not yet be known.

Acknowledgements

The authors are employees of Actelion Pharmaceuticals Ltd., the manufacturer of bosentan and sponsor of the systems described in this article.

The input of D. Pittrow, MD, PhD, Institute for Clinical Pharmacology, Technical University of Dresden to various sections of the manuscript is appreciated. We also acknowledge the input of Ralph Stadler, Senior Consultant, IBR AG to the TRAX system.

References

1. Strom BL. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: a counterpoint. JAMA 2004; 292 (21): 2643-6
2. Fontanarosa PB, Rennie D, DeAngelis CD. Postmarketing surveillance: lack of vigilance, lack of trust. JAMA 2004; 292 (21): 2647-50
3. Centers for Education and Research on Therapeutics (CERTs) Risk Assessment Workshop Participants. Risk assessment of drugs, biologics and therapeutic devices: present and future issues. Pharmacoepidemiol Drug Saf 2003; 12 (8): 653-62
4. Strom BL, Tugwell P. Pharmacoepidemiology: current status, prospects, and problems. Ann Intern Med 1990; 113: 179-81
5. Rawlins MD. Pharmacovigilance: paradise lost, regained or postponed? The William Withering Lecture 1994. J R Coll Physicians Lond 1995; 29: 41-9
6. Food and Drug Administration (FDA) Working Group. PhRMA/FDA/AASLD drug-induced hepatotoxicity white paper: postmarketing considerations, November 2000 [online]. Available from URL: http://www.fda.gov/cder/livertox/postmarket.pdf [Accessed 2005 Mar 4]
7. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med 2004; 351: 1425-36
8. Rubin LJ. Primary pulmonary hypertension. N Engl J Med 1997; 336 (2): 111-7
9. Galie N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension: the Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J 2004; 25 (24): 2243-78
10. Channick RN, Sitbon O, Barst RJ, et al. Endothelin receptor antagonists in pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43 (12 Suppl. S): 62S-7S
11. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002; 346 (12): 896-903
12. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension; a randomised placebo-controlled study. Lancet 2001; 358 (9288): 1119-23
13. Actelion Pharmaceuticals US, Inc. Tracleer® product information [online]. Available from URL: http://www.tracleer.com/TRALibrary/TRALib004/TRALib004PrescribingInfo.html [Accessed 2005 Sep 28]
14. Actelion Pharmaceuticals UK. Tracleer® EU summary of product characteristics, 2004 [online]. Available from URL: http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=10231 [Accessed 2005 Sep 28]
15. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med 1991; 115 (5): 343-9
16. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005; 25 (2): 244-9
17. 5th PSUR Tracleer®. Allschwil: Actelion Pharmaceuticals Ltd, 2005 Jan
18. 7th TRAX PMS data report to CHMP for the cumulative period from 24 May 2002 to 19 November 2004. Allschwil: Actelion Pharmaceuticals Ltd, 2005 Feb 1. (Data on file)
19. Zimmerman H. Drug-induced liver disease. Clin Liver Dis 2000; 4 (1): 73-96
20. Zimmerman H. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia (PA): Lippincott Williams & Wilkins, 1999
21. Food and Drug Administration (FDA) Working Group. CDER-PhRMA-AASLD Conference 2000: clinical white paper. Food and Drug Administration, Rockville, USA [online]. Available from URL: http://www.fda.gov/cder/livertox/clinical.pdf [Accessed 2005 Sep 12]

Correspondence and offprints: Dr *Eleanor S. Segal*, Global Drug Safety, Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, CH-4123 Allschwil, Switzerland.
E-mail: Eleanor.Segal@actelion.com