BMJ 2016;353:i2978 doi: 10.1136/bmj.i2978 (Published 22 June 2016)

ANALYSIS

Letting post-marketing bridge the evidence gap: the case of orphan drugs

Post-approval studies seldom cover the deficit of knowledge about orphan drugs, find **Roberta Joppi and colleagues**

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Developing medicines for rare diseases is difficult. Small target populations limit the potential to recover investments in research and development, and even when medicines get to clinical trials, there may be too few patients to support adequately sized trials. Trials for these drugs often also have other shortcomings—for example, the use of placebo as control, surrogate endpoints instead of hard clinical outcomes, or an inadequate length of follow-up. As a result, orphan drugs—those intended for rare diseases (box 1)[1]—are not only few but often have insufficient evidence of efficacy and safety at the time of approval.[2]

Regulation introduced in Europe in 2000 aimed to encourage research and development into orphan drugs.[1] The regulation did not substantially improve the evidence underlying their approval[2-4] but allowed regulators to grant marketing authorisation trusting that post-marketing research would bridge the gap of knowledge on their safety and effectiveness. To check whether those expectations are being met and the missing data provided, we examined the evidence generated in the 10 years after marketing authorisation for orphan products approved in a single year.

Available evidence before and after marketing

We analysed all six orphan products authorised by the European Medicines Agency (EMA) in 2004 (table 1⇓) and conducted a literature search for studies of these drugs up to December 2014. We systematically searched MedLine, Embase, and Cochrane databases for published randomised clinical trials, observational studies, and meta-analyses of the selected products using their name or MESH term(s), and their authorised or designated indication(s). After a library search, two reviewers independently screened abstracts and full texts, and separately extracted data. Discrepancies were solved by consensus. We considered 10 years sufficient time to answer the clinical questions still open at the time of approval. It is also the period covered by patent and the special protection reserved for licensed orphan products, and companies should still be interested in increasing the evidence relating to their products.

Here, we summarise the evidence available before and after approval for each of the drugs.

Anagrelide

Anagrelide was authorised for the treatment of essential thrombocythaemia on the basis of two compassionate use programmes verifying platelet count reduction in 1176 patients overall. Three further studies (the intended phase II, single arm, pivotal study; another uncontrolled study; and a randomised comparative trial against hydroxyurea) were either stopped early or reported unreliable efficacy and safety data according to good clinical practice inspectors.[5]

Of the eight post-marketing studies,[6-13] three compared anagrelide and hydroxyurea. In the largest phase III trial anagrelide was worse than hydroxyurea in preventing arterial and venous thrombotic events, serious haemorrhage, and death in 809 patients with essential thrombocythaemia (odds ratio =1.57; 95% confidence interval 1.04 to 2.37; P=0.03).[6]

Two further trials primarily examined reduction in platelet count. However, one small trial also reported no thrombotic events with anagrelide and 11 with hydroxyurea.[7] In one non-inferiority trial anagrelide seemed to be as effective as hydroxyurea in preventing thrombocythaemia related clinical events, though the wide confidence intervals indicate that it could be much better or much worse than placebo (hazard ratio=0.92; 95% CI 0.57 to 1.46).[8]

How the evidence changed—At the time of approval it was known that anagrelide reduced platelet count but not what its effects were on thrombotic or haemorrhagic complications of essential thrombocythaemia or whether it was better than other platelet reducing agents. Post-marketing studies indicate that

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Box 1: Definition of "orphan medicinal product"

European regulation No 141/2000 says that a medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

a) that it is intended for the diagnosis, prevention, or treatment of a life threatening or chronically debilitating condition that affects ≤5 in 10 000 persons in the EU when the application is made or for which marketing is unlikely to generate sufficient return on investment without incentives

b) And that no satisfactory method of diagnosis, prevention, or treatment of the condition has been authorised in the EU or, if such method exists, that the medicinal product will be of significant benefit to those affected by the condition

anagrelide is probably worse than hydroxyurea in reducing thrombocythaemia related vascular events but no regulatory action has been taken.

Cladribine

Cladribine was approved for patients with hairy cell leukaemia on the basis of two single arm studies reporting inconsistent overall response rates (97% and 19%). No overall survival figures were collected.[14]

After marketing approval two studies[15 16] found no difference in response rates and toxicity with the daily and weekly schedules of cladribine. Another phase II single arm study[17] assessed responses and bone marrow minimal residual disease in 36 patients given five daily cladribine doses followed one month later by eight weekly rituximab doses. Persistent disease was reported in 12/27 evaluable patients (44%) given cladribine, while none had persistent disease after rituximab.

How the evidence changed—Post-marketing studies did not help clarify clabribine's relative efficacy and place in therapy with respect to rituximab or the inconsistent findings on the response of the disease.

Ibuprofen

Ibuprofen solution (Pedea) was approved for patent ductus arteriosus in preterm newborns on the basis of a meta-analysis of six randomised controlled trials comparing it with indomethacin.[18] The meta-analysis, which was conducted by the company itself, concluded that ibuprofen and indomethacin were equivalent with regard to ductal closure (75% *v* 73%, odds ratio=1.14, 95% CI 0.73 to 1.77), requirement for surgical ligation (11.7% in both groups, odds ratio=1.00, 0.55 to 1.81), and perinatal mortality (10.1% *v* 9.1%, hazard ratio=1.11, 0.55 to 2.24). The regulatory dossier also included a dose-range study[18] and a double blind randomised trial of prophylactic ibuprofen versus placebo in neonates with gestational age less than 28 weeks.[18] Of the 47 infants who reached 36 weeks of gestational age, none in the ibuprofen group and five in the placebo group required surgery. Ibuprofen was not recommended for prophylactic use because the possible small advantage in avoiding surgery was counterbalanced by higher risks of renal failure and pulmonary adverse events without a survival advantage. The trial was stopped at 60% of recruitment.

After the marketing authorisation, five small single centre trials,[19-23] two systematic reviews with meta-analyses,[24 25] and one observational study[26] were published. One of the trials found that continuous infusion of ibuprofen was more effective and just as safe as the bolus dose; in a second trial ibuprofen proved as effective as indomethacin, while in two trials paracetamol was as effective as ibuprofen but safer. In the last trial ibuprofen caused more renal impairments than placebo in neonates with gestational age less than 27 weeks and in low birthweight infants. The observational study found that oral ibuprofen caused no fewer neurological or cognitive impairments than intravenous ibuprofen.[26]

Of the two meta-analyses, one showed that oral ibuprofen gave a higher ductal closure rate than intravenous ibuprofen but the rate was similar to intravenous indomethacin.[24] The second meta-analysis concluded that ibuprofen was as effective as indomethacin and possibly there was less risk of necrotising enterocolitis and transient renal insufficiency.[25]

How the evidence changed—At the time of approval ibuprofen was known to be no better than indomethacin for patent ductus arteriosus. Post-marketing data showed its renal toxicity in newborns with gestational age less than 27 weeks. Information about the long term neurological and pulmonary safety of ibuprofen relies on one observational study. The news was that paracetamol was as effective as ibuprofen but less toxic, but this was never taken into account.

Mitotane

Mitotane was approved for advanced adrenal cortical carcinoma on the basis of 18 uncontrolled studies, mostly retrospective case series.[27] Only a few studies had evaluated the efficacy of mitotane on survival with respect to activity, and their results were contradictory.

The post-marketing research included one randomised trial,[28] two single arm studies (one phase I[29] and one phase II[30]), and one observational study.[31] The randomised trial[28] showed no difference in overall survival in patients treated with mitotane-etoposide-doxorubicin-cisplatin or mitotane-streptozocin (14.8 months and 12.0 months, respectively; hazard ratio=0.79, 95% CI 0.61 to 1.02; P=0.07). The phase I, single arm trial of the combination of mitotane and cixutumumab was terminated on account of toxicity.[29] The phase II uncontrolled study[31] found complete response in only 5/72 patients. The observational study[31] showed that only patients receiving early specialised care survived longer.

How the evidence changed— None of the studies showed any survival benefit with mitotane.

Porfimer sodium

Porfimer was approved for photodynamic treatment of Barrett's oesophagus. Clinical data in the regulatory dossier came from one randomised trial and two single centre, uncontrolled studies.[32] In the controlled trial complete ablation of dysplasia was more common with porfimer plus omeprazole than omeprazole alone (76.8% *v* 38.6% at 24 months).

Three randomised trials were published post-marketing,[33-35] together with two dose escalation studies[36] and one observational retrospective study published as an abstract.[37] In one trial porfimer plus omeprazole reduced the risk of adenocarcinoma more than omeprazole alone (13% *v* 20%, P=0.006 at two years and 15% *v* 29%, P=0.004 at five years).[33] The second trial found argon plasma coagulation and porfimer sodium equally effective in eradicating Barret's mucosa.[34] The final trial[35] found no difference in efficacy and safety of photodynamic treatment with 5-aminolaevulinic acid or porfimer.

How the evidence changed—Post-marketing studies confirmed the better efficacy of porfimer as an add-on to omeprazole and contributed slightly to defining its role in treatment relative to other options such as 5-aminolaevulinic acid and argon plasma coagulation. Unfortunately, porfimer was withdrawn from the market in 2012 because of reports suggesting it caused deep vein thrombosis.[32]

Zinc acetate dehydrate

Zinc acetate dehydrate was approved for Wilson's disease, an autosomal recessive defect in hepatic excretion of copper, on the basis of long use in clinical practice as a maintenance treatment. Other zinc salts had long been used to reduce the intestinal absorption of copper. The marketing authorisation was granted on the basis of data accumulated over more than 40 years.[38] Most came from a cohort of 148 patients treated with zinc since the 1980s.[39] The evaluation was based on an overall clinical impression of lack of disease progression.

The dossier also included uncontrolled studies and one trial using zinc sulphate (the two zinc salts are pharmacologically comparable and they are dealt as such in the European public assessment report).[38] The one non-randomised trial of zinc sulphate versus penicillamine was in 67 newly diagnosed patients, 56 of whom had symptoms.[38] Improvement was reported in 15 patients in the zinc group and 14 in the penicillamine group, and deterioration in, respectively, two and three patients from the two groups.

How the evidence changed—Post-marketing studies suggest that zinc has similar efficacy to penicillamine in Wilson's disease and lower toxicity than other copper chelators. Despite this, no post-marketing head to head trials have been done.

Need for change

Our analysis shows that post-marketing clinical research did not satisfactorily cover the deficit of knowledge about orphan products at the time of their licensing in 2004. Furthermore, manufacturers were not obliged to carry out further studies. Despite lack of evidence, the original regulatory decisions were not revised and all the products except porfimer are still on the market. The US Food and Drug Administration also approved these drugs with no post-marketing commitments, and all of them are still on the US market.

The present situation is concerning. Licensing of orphan products with no or incomplete proof of their efficacy and safety, sometimes even relative to other available treatments, may unduly harm patients and waste health service resources.[40] EU regulation stipulates that new medicines are approved on the basis of proved quality, efficacy, and safety, but few licensed orphan products meet these criteria.[41] Moreover, the regulation on orphan products allows market exclusivity only for new products that are shown to be "clinically superior" to competitors already on the market.[1] This is difficult to achieve without comparative trials that have clinically meaningful outcomes.

These problems apply to any medicine approved on the basis of insufficient evidence, not just orphan products.[40] Moves to abridge and simplify the evaluation of new medicines, such as conditional approvals and adaptive licensing, should therefore be approached with caution.[42] Whenever the efficacy or safety of an orphan product is not clear, the EMA should require further clinical research—for example, to prove real clinical benefit in the long term instead of surrogate advantages in a limited time frame. Evidence should be provided well before the 10 year market protection expires. If the company does not comply with the EMA's requests, the agency should withhold its marketing authorisation, engage an independent institution to complete the requested studies, and in the meantime ensure the drug is available to currently treated patients through an expanded access programme.

Contributors and sources: All authors have experience in regulatory policy, SG and VB being members of Italian and European drug committees, and in research methodology and assessment of new drugs. All authors participated in each draft of the article and its edits. RJ and CG reviewed all the European Public Assessment Reports on the evaluated drugs; RJ and CG systematically searched MedLine, Embase, and Cochrane databases for published randomised clinical trials, observational studies, and meta-analyses; RJ and CG independently screened abstracts and full texts, and separately extracted data; VB and SG reviewed extracted data. SG is guarantor.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare

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Key messages

Authorisation of drugs for rare diseases with unmet treatment needs relies on post-marketing research to cover incomplete information

However, questions about safety and effectiveness are seldom settled in the post-marketing phase

Ongoing uncertainty about these drugs may harm patients and waste health system resources

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Table

Table 1| Evidence available before and after marketing for six orphan drugs approved in 2004

Orphan drug (disease)	Best available evidence		Type of evidence (GRADE level)	
	Before	After	Before	After
Anagrelide (essential thrombocythaemia)	Platelet count reduction	More vascular events than with adequate comparator*	Case series (4)	Superiority RCT (2b)
Cladribine (hairy cell leukaemia)	Inconsistent response rates (19-97%)	56% responses after cladribine became 100% after rituximab†	Case series (4)	Case series (4)
Ibuprofen (patent ductus arteriosus (PDA))	As effective as indomethacin in closing PDA	As effective as indomethacin in closing PDA, but less necrotising enterocolitis and transient renal insufficiency†	Meta-analysis of RCT (1a)	Systematic review with meta-analysis of RCT (1a)
Mitotane (adrenal cortical carcinoma)	Response rate 20-30%	Response rate 48.6%†	Case series (4)	Case series (4)
Porfimer sodium (Barrett's oesophagus)	More frequent ablation of dysplasia as add-on to omeprazole	Reduced risk of adenocarcinoma as add-on to omeprazole‡	RCT (1b)	RCT (1b)
Zinc acetate (Wilson's disease)	Prevents progression of disease	None†	Case series (4)	None

Case series means uncontrolled studies. RCT=randomised controlled trial. GRADE rating of evidence ranges from 1 (highest) to 5.

*Post-marketing trial shows worse efficacy.

†Evidence unchanged.

‡Post-marketing studies show better efficacy but drug withdrawn for safety reasons.