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SPECIAL ARTICLE

The Italian Horizon Scanning Project

Roberta Joppi · Luca Demattè · Anna Michela Menti · Daniela Pase · Chiara Poggiani · Luigi Mezzalira · on behalf of the Italian Horizon Scanning Project Group

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Introduction

Demographic changes, increased life expectancy and the accelerated development of new health technologies have a considerable impact on National Health Systems (NHSs) worldwide [1].

According to the Pharmaceutical Research and Manufacturers of America (PhRMA) more than 2700 new molecules for 4600 indications are currently under development [2].

Why an early assessment of emerging drugs?

The often modest therapeutic value, the great uncertainty in terms of level of innovation, and the high cost of new medicines [3–5] suggest a pressing need for an early evaluation of emerging pharmaceuticals.

Health Technology Assessment (HTA) is a form of policy research that studies the short- and long-term consequences of introducing health technologies in a healthcare system in terms of safety, clinical benefit, and social-economic aspects, thereby providing decision-makers with important information [6]. However, this kind of evaluation is carried out only after the launch of new technologies, which prevents the implementation of management strategies. Thus, methods for identifying and timely assessing new technologies are necessary to help decision-makers plan their appropriate use and optimize resources [7, 8].

On the basis of these considerations an early warning system for identification and assessment of emerging technologies could provide decision-makers with timely information on the potential clinical impact and cost effectiveness of new health technologies.

The Italian Horizon Scanning Project (IHSP) predicts which new drugs are likely to have a significant impact on the Italian NHS, issuing periodical evaluations of emerging medicines for which a European Marketing Authorization (M.A.) is expected within 12–36 months. The IHSP is a member of the EuroScan, an international collaborative network of Early Warning Units established in 1999 for the identification and assessment of emerging new technologies [9].

How does IHSP work?

The IHSP collects information on emerging medicines from websites (pharmaceutical companies, financial analysis companies, international scientific societies, international regulatory authorities, health information websites, etc.), medical–scientific literature, pharmaceutical companies' press releases, and other early warning systems. A scientific committee, a database team, and an evaluation team for emerging pharmaceuticals, with a technological infrastructure for data collection, checking, monitoring, and analysis

R. Joppi (✉) · A. M. Menti · D. Pase · C. Poggiani · L. Mezzalira
Pharmaceutical Department, Local Health Unit of Verona,
Via Salvo D'Acquisto 7,
37122 Verona, Italy
e-mail: roberta.joppi@ulss20.verona.it

L. Demattè
CINECA–Consortium of Universities,
Via Magnanelli 6/3,
40033 Casalecchio di Reno, BO, Italy

all support IHSP's activities. The database is available on the web, with restricted access [10].

The scientific committee (IHSP-SC) includes regional and national stakeholders with nationally and internationally recognized experts in drug evaluation. It assigns a priority to emerging drugs according to their possible M.A. date and their potential grade of innovation [11, 12], therapeutic and economic impact, possible price, and NHS sustainability. Other tasks include the revision of all assessments produced, decisions on their dissemination, identification of possible therapeutic needs and priority research areas for the Italian NHS, and the development of links with other NHS institutions, scientific associations, and international groups.

The IHSP database team (IHSP-DT) includes Internet technology (IT) people and a scientific secretariat (pharmacists and an administrative employee). Its tasks are to collect information, maintain and update the database, guarantee the confidentiality of the data stored, support the production of the assessment reports on emerging medicines, and provide IHSP-SC and/or the IHSP evaluation team (IHSP-ET) with any additional documents required.

The IHSP-ET for emerging medicines comprises a panel of about 50 clinicians with expertise in different medical and surgical fields, and a scientific secretariat. The IHSP-ET produces the New Product Information Report (NPIR).

The IHSP is currently funded publicly, and private sponsors are accepted only if they have no conflict of interest. It is generally understood that private funds should represent only a minority share in the global IHSP financial resources.

Which drugs have been identified to date?

From January 2007 to December 2008, the IHSP has entered 778 drugs in development (phase I onwards) into its database, corresponding to 1615 items (i.e., new chemical entities, new indications, new formulations, new associations, and new dosages). At the present time, 42.7% of the drugs are in phase II of development and 45% in phase III. Ninety-one and 103 medicines are at the pre-registration stage in the European Union and USA, respectively.

Table 1 shows the drugs in development grouped according to their Anatomical and Therapeutic Chemical Classification (ATC), and the number of molecules in phase II and III of development in Europe related to each ATC group.

Which reports are issued by the IHSP?

The IHSP produces three different reports, which appear 36, 18, and 12 months, respectively, before the European M.A. date. The report issued 36 months before the potential M.A. date provides information on the mechanism of action of an emerging drug, phase II trials, which are then often available, and the indications of ongoing phase III trials. All of this information is recorded in national and international clinical trial registries. This report provides the Italian

Table 1 Drugs in development in the IHSP database grouped according to ATC group and stage of development

ATC code (I level)	Drug group	USA + EU, *n*	EU, *n*	EU phase II, *n* (%)	EU phase III, *n* (%)
L	Antineoplastic and immunomodulating agents	613	217	87 (40.1)	102 (47)
N	Nervous system	243	84	29 (34.5)	40 (47.6)
A	Alimentary tract and metabolism	168	60	16 (26.7)	33 (55)
J	Anti-infectives for systemic use	144	58	14 (24.1)	30 (51.7)
C	Cardiovascular system	93	48	19 (39.6)	23 (47.9)
B	Blood and blood forming organs	95	43	15 (34.8)	20 (46.5)
M	Musculo-skeletal system	67	53	5 (9.4)	12 (22.6)
R	Respiratory system	53	21	8 (38.1)	8 (38.1)
G	Genito-urinary system and sex hormones	43	16	6 (37.5)	7 (43.7)
D	Dermatologicals	32	13	5 (38.5)	7 (53.8)
V	Various	22	5	0	5 (100)
S	Sensory organs	27	3	1 (33.3)	2 (66.6)
H	Systemic hormonal preparations, excluding sex hormones and insulins	10	3	0	2 (66.6)
P	Antiparasitic products, insecticides and repellents	5	1	0	1 (100)
Total		1615	625	205 (32.8)	292 (46.7)

IHSP, Italian Horizon Scanning Project; ATC, Anatomical and Therapeutic Chemical Classification system; EU, European Union

Table 2 Examples of the most interesting drugs assessed by the IHSP in 2008

Drug	ATC	Proposed indication	Mechanism of action	Comments	NPIR
Drugs listed in the report issued 36 months before an M.A.					
Apixaban	B01A	Prevention of stroke and systemic thromboembolism in patients with atrial fibrillation	Pyrazole-based factor Xa inhibitor	Potential high economic impact on the NHS. The development program includes a large pivotal trial (15,000 patients) comparing apixaban vs. warfarin (current gold standard)	
Bevacizumab	L01XC07	Advanced gastric cancer (first line therapy in combination with cis-platin and capecitabine)	IgG1 monoclonal antibody-VEGF antagonist	Potential high impact on the NHS (in Italy 17,000 new cases per year; the indication corresponds to 23% of all tumors). Bevacizumab could be added to standard chemotherapy in HER2-negative disease, about 78% of stomach tumors	
Dapagliflozin	A10X	Type-2 diabetes mellitus	Sodium glucose co-transporter type 2 inhibitor	New drug class and mechanism	
Deforolimus	L01	Bone sarcoma	Inhibitor of the mammalian target of rapamycin (mTOR) and VEGF in cells PTEN-mutated	Extremely rare and devastating neoplasm (100 new cases per year in Italy).	
Lisdexamfetamine	N06B	Attention-deficit hyperactivity disorder (in children)	Psycostimulant prodrug obtained by conjugation of amphetamine with aminoacids.	New drug class alternative to amphetamine-based therapy	
Drugs listed in the report issued 18 months before an M.A.					
Dabigatran	B01A	Stroke prevention in atrial fibrillation	Reversible thrombin inhibitor	1) High impact on the NHS; pivotal trial includes 18,000 patients 2) Possible competitor of warfarin	Produced
Denosumab	M05	Postmenopausal osteoporosis (treatment and prevention)	Anti-RANKL monoclonal antibody inhibiting osteoclast differentiation and maturation	Potential high patient impact due to its pharmacokinetics profile (subcutaneous administration twice yearly) with respect to biphosphonates	Produced
Dronedarone	C01BD	Atrial fibrillation	Class III-antiarrhythmic as amiodarone	Potential improved safety profile with respect to amiodarone	Produced
Glatiramer acetate	L03AX13	Treatment of patients with first clinical event suggestive of multiple sclerosis	T helper cells modulator and inducer of expression of brain-derived neurotrophic factor	1) Weak evidence: results of an interim analysis from the pivotal phase III trial are only available 2) Patent expiry for multiple sclerosis in 2012 in EU and in 2014 in USA	Produced
Liraglutide	A10BX07	Type 2 diabetes mellitus	Incretin mimetic acting as analogue of glucagone-like peptide-1	It is expected to have a similar impact on NHS with respect to its analogues (vildagliptin, sitagliptin and exenatide), which are already monitored by the Italian Medicines Agency (not prioritized)	Not produced
Plerixafor	L03A	Stem cell transplantation in patients	Mobiliser of CD34+ hematopoietic stem cells,	It represents a potential innovative option	Produced

Table 2 (continued)

Drug	ATC	Proposed indication	Mechanism of action	Comments	NPIR
		with non-Hodgkin's lymphoma and multiple myeloma	through reversible inhibition of their CXCR4 chemokine surface receptor	for non-responder to standard therapy (granulocyte-colony stimulating factor) for stem cell mobilization aimed to autologous stem cell transplantation (unmet medical needs)	
Silodosin	G04C	Benign prostatic hyperplasia	Selective α1a-adrenoceptor antagonist	Similar to other drugs with same mechanism of action (me-too). (not prioritized)	Not produced
Tolvaptan	C03XA01	Congestive heart failure and hyponatremia	Selective vasopressin V2 receptor antagonist	1) Diuretic with a new mechanism of action and a potential improved safety profile due to absence of electrolyte depletion or activation of neurohormonal system 2) It has been compared only with placebo for congestive heart failure in a noninferiority phase III trial [23] in 4,133 patients (EVEREST) and for hyponatremia in two phase III trials [24] in overall 448 patients (SALT-1 and SALT-2)	Produced

NPIR, New Product Information Report; NHS, National Health System

Medicines Agency (AIFA) with information on the development plans of emerging drugs. Since AIFA directly funds an independent research program, this kind of information is useful in identifying research areas that are interesting to the Italian NHS but which are not met by the pharmaceutical companies. The report produced 18 months before an M.A. assesses available results of the first phase III completed trials, which enables the identification and prioritization of emerging medicines likely to have a clinical and economical impact on the Italian NHS. Thus, this report is not specifically addressed to policy-makers, but is essentially utilized for internal purposes, similarly to processes carried out in other countries. The assessment report issued 12 months ahead of the possible licensing date, the New Product Information Report (NPIR), critically reports on available data on efficacy and safety of the new medicine, its possible advantages over existing treatments (level of innovation), its possible place in therapy, estimated direct costs, and information on other potentially relevant indication(s) in development or on competitors in development for the same indication. At this stage, any changes in the prescription details can also be assessed by using historical prescription data on available treatments and by defining the target population according to the inclusion/exclusion criteria and the results of the trial(s). The NPIR report and the transferability analysis are particularly useful to decision-makers as they provide information that can be used to improve planning and optimize the most appropriate use of resources and to decide upon the level of reimbursement of a new drug and possible limitations in its prescription.

How does IHSP prioritize emerging medicines?

Prioritization has always been a critical step in selecting technologies to be assessed for HTA purposes, and a variety of different approaches have been adopted by different agencies worldwide due to different healthcare pressures. In the same way, a Horizon Scanning System has to assign a priority to emerging drugs according to NHS needs [13, 14]. The criteria adopted by the IHSP-SC are related to the burden of the specific disease and to the efficacy, safety, and compliance of the emerging drug compared to available treatments, to the potential social, economic, and organizational impact of the new medicine on the Italian NHS, and to its possible M.A. date. For a drug to be prioritized, efficacy/safety results of phase III trials (phase II trials for certain anticancer drugs) and a possible M.A. date are essential. As a second step, epidemiology of the disease and potential organizational/social consequences of the emerging medicine are evaluated. Finally, the economical aspects (direct costs, when available) of new therapeutic agents are examined.

The IHSP-SC has resolved not to rate the reported items or to establish a threshold for drugs to be prioritized. Instead, it has decided to utilize these criteria very pragmatically for 2–3 years. After this period, the adequacy of the criteria adopted to identify products of major interest and their initial impact on the NHS will be retrospectively verified. This analysis will suggest any points in the prioritization process that can usefully be revised.

Looking into the future

In 2008, IHSP assessed 20 drugs for which a European M.A. was expected within 36 months, 36 medicines for which an M.A. was expected within 18 months, and eight pharmaceuticals for which an M.A. was expected within 12 months. Table 2 highlights some examples of the most interesting drugs from among those identified and evaluated. For each drug, a short comment is reported. In general, for the majority of drugs evaluated, there are critical limitations in the development programs, such as the use of a non-inferiority design, placebo as comparator, or non-validated surrogate endpoints. These shortcomings in the approach that has been used by pharmaceutical firms for the last 10 years for developing new pharmaceuticals [3–5] still makes it difficult to define their level of innovation and thus their possible place in therapy.

Prasugrel: an example of early critical appraisal and impact analysis

In 2007, a new antiplatelet agent, prasugrel, was identified by searching ad hoc websites (BioSpace, WalGreens Health Service, Drug Companies, etc.) and pharmaceutical bulletins (Scrip, etc.), and subsequently entered into the IHSP-database. A preliminary assessment report was issued about 18 months before its hypothetical M.A.. The CS-IHSP has prioritized prasugrel because its efficacy appears to be superior to clopidogrel; at the same time, its antiplatelet activity is associated with an increased risk of bleeding.

After six months IHSP produced the full assessment report (NPIR). Prasugrel appears to be superior to clopidogrel in the pivotal trial TRITON-TIMI [15]. However a comparison of prasugrel to high-dose clopidogrel would be useful to better define the superiority of the investigational drug. The new anti-platelet drug has shown a significant higher efficacy in diabetic as opposed to non-diabetic patients. Although the subgroup was prespecified and robust (n = 3146 patients), randomization was not stratified by diabetic status, and the possibility of an unidentified imbalance between treatment groups exists [16]. The antiplatet activity of the new drug is associated with an increased risk of bleeding. Safety is an issue that needs to be more carefully addressed as the post-hoc analyses performed for the TRITON study are still

unsatisfactory in identifying patients at increased risk for bleeding, namely, patients older than 75 years, with low body weight and with history of stroke/transient ischemic attack.

In addition to the critical appraisal, IHSP performed an impact analysis aimed at evaluating the potential target population and the possible future prasugrel consumption in the Italian setting. Taking into account the inclusion criteria of the TRITON-TIMI trial, the possible target population was identified from the ARNO database [17]. Data for 2005 on dual antiplatelet therapy (clopidogrel or ticlopidine + acetylsalicylic acid) prescriptions and hospital discharge after percutaneous coronary intervention (PCI) with stent insertion were evaluated. Figure 1 shows the transferability model IHSP has developed. From the ARNO database, the incidence rate for stent insertion is about 2/1000 Italian citizens. The Italian population is 60,000,000, with about 120,000 patients per year receiving PCI with stent insertion; of the latter, 16.5% are diabetics. The ARNO data show that among the non-diabetics, 43% are currently treated with clopidogrel for up to 12 months. Assuming that 50% of the non-diabetics currently receiving clopidogrel and the whole diabetic population can be shifted to prasurel, about 41,000 patients per year were estimated to be potential users of the new antiplatelet agent. Foreseeing that the therapy duration should be the same as with clopidogrel, prasugrel consumption could be of about 11 million defined daily doses per year. If antiplatelet therapy duration were to be doubled for patients receiving a drug-eluting stent [18, 19], prasugrel consumption could be of about 15 million DDD yearly.

This impact analysis is speculative and has limitations. In fact, the results observed in the diabetic population are methodologically weak, but they are likely to be widely used as an "advertising message". For this reason, it is important to provide policy-makers with information on a possible scenario of the future market.

Italian Horizon Scanning system: not only a forecasting tool

Early warning systems were developed to support policy-makers in their decisions since HTA could not provide them

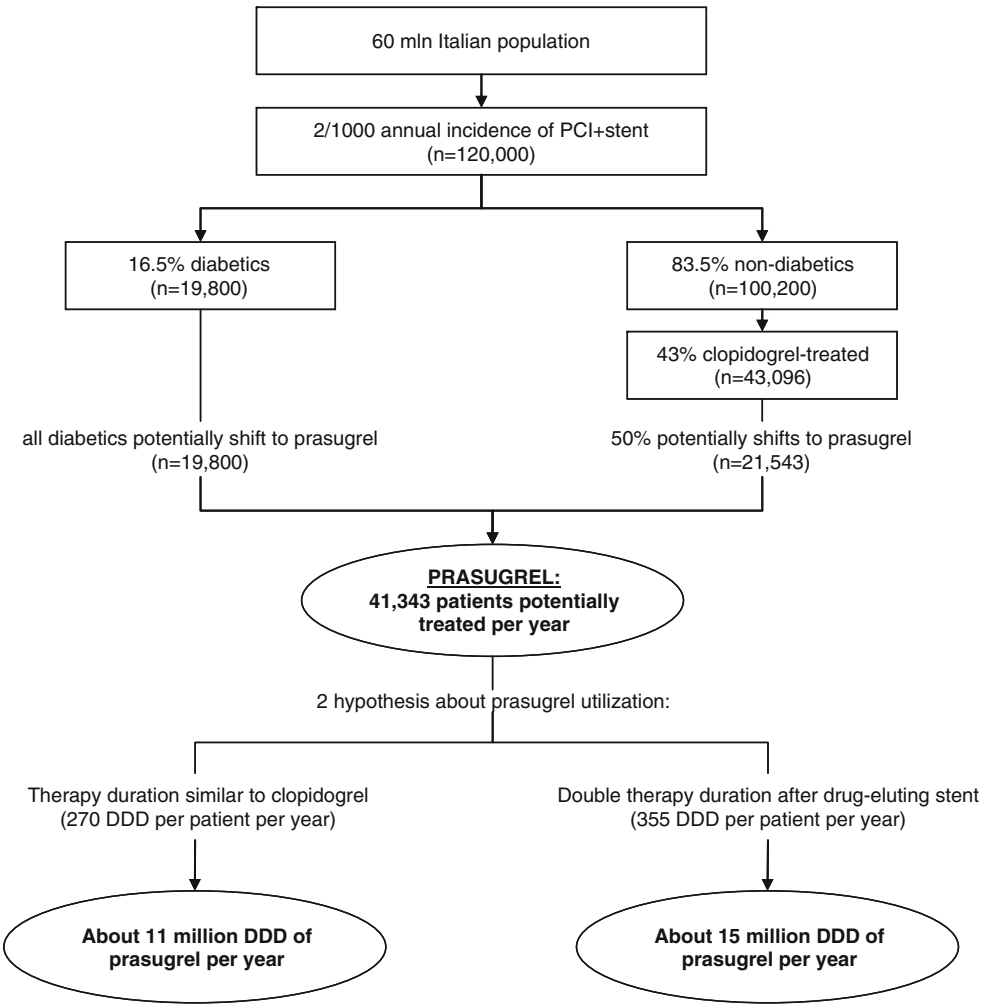

Fig. 1 Transferability/impact analysis model developed by the Italian Horizon Scanning Project. *DDD* Defined daily doses, PCI percutaneous coronary intervention

with timely information. In addition to this important role in predicting the impact of emerging technologies on the NHS, Horizon scanning can also foster a constructive debate on development plans of new drugs in terms of the interests of NHSs and highlighting research needs for further investigation.

Once a product has reached the market, early warning systems can retrospectively track its development, identifying the studies reported in clinical trials registries and verifying which ones were completed, published, or included in the registration dossier. This could be of particular interest in view of the recent debate on discrepancies between the trial information reviewed by the regulatory agencies and information found in published trial reports, on the limited and incomplete public access to clinical trial results to be found on the "Product Label" (Federal Drug Agency) or in the European Public Assessment Report (EMEA), and on requirements for study results to be posted in the Clinical Trials Registry [20–22].

Italian horizon scanning group

Scientific Committee Antonio Addis, Alessandro Battaggia, Vittorio Bertele', Luigi Bozzini, Pietro Folino Gallo, Teresa Gasparetto, Claudio Graiff, Anna Grion, Roberta Joppi, Luigi Mezzalira, Luigi Pagliaro, Vittorio Pengo, Giovanna Scroccaro, Mara Vezzani.

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Conflict of interest None

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