Acta Poloniae Pharmaceutica – Drug Research, Vol. 71 No. 2 pp. 329–335, 2014 ISSN 0001-6837
Polish Pharmaceutical Society

GENERAL

CONSUMPTION OF OSTEOANABOLIC DRUGS AND STRONTIUM RANELATE IN THE TREATMENT OF OSTEOPOROSIS IN THE CZECH REPUBLIC IN 2005–2011

LEOS FUKSA[1], MAGDA VYTRISALOVA[1]*, TEREZA HENDRYCHOVA[1], IVANA HRUBESOVA[1], JIRI VLCEK[1] and VLADIMIR PALICKA[2]

[1]Department of Social and Clinical Pharmacy, Faculty of Pharmacy in Hradec Kralove, Charles University in Prague, Heyrovskeho 1203, 500 05 Hradec Kralove, Czech Republic
[2]Osteocentre, Institute of Clinical Biochemistry and Diagnostics, Charles University in Prague, Faculty of Medicine and University Hospital in Hradec Kralove, Czech Republic

Abstract: Anti-osteoporosis drugs with osteoanabolic (teriparatide, intact parathormone) and dual (strontium ranelate) mechanism of action are currently available for the treatment of postmenopausal, glucocorticoid induced or male osteoporosis in the Czech Republic (CZ). These expensive drugs are subjects of special prescribing limitations (2nd line treatments). The objective was to analyze trends in consumption of osteoanabolic and dual drugs in the treatment of osteoporosis since their introduction onto the market in CZ (2005–2011). The prescription-based database of the General Health Insurance Company of the Czech Republic that covers approximately 60% of the Czech population was used as the data source. An insured person with a recorded prescription for teriparatide (TRPD), intact parathormone (iPTH) or strontium ranelate (SR) in the period of interest was defined as a patient; 271 (224), 77 (75) and 5930 (5545) patients (women) treated with TRPD, iPTH and SR in 2011, respectively, were identified. The median age of patients on TRPD and SR ranged from 71 to 74 years in 2006–2011. The number of patients treated with TRPD between 2009 and 2011 has been stable, while in iPTH the number increased 2.8 times in the same time period. The number of patients treated with SR has been steadily rising since its introduction in 2005. SR was prescribed most often by physicians specialized in internal medicine (42%) and rheumatology (25%). Male patients accounted for 6% of the SR consumers in 2011. The consumption of dual and osteoanabolic drugs has been rapidly increasing. Consumption rates in men (both absolute and relative) have been increasing but still remain relatively low.

Keywords: drug consumption, drug prescription, osteoporosis, strontium ranelate, teriparatide, intact parathormone, osteoanabolic drugs, prescription-based database

Prevalence of osteoporosis (OP) has been significantly increasing together with aging of the population. In the Czech Republic (CZ), OP affects more than 400,000 women and 200,000 men. Prevalence of OP in CZ female and male population aged 50 or more amounts to 20.4% and 6%, respectively. Expenditures related to OP form an essential part of health-care budgets due to rising costs associated with low-trauma fractures. The age-standardized hip fracture rates (100,000/year) in CZ in 2010 was 374 for women and 211 for men. Incidence of hospitalization for hip fractures more than doubled in CZ from 1981 to 2009. During 1997–2007, the average year-to-year increase in the number of hip fractures in CZ has been estimated as 5.9% (1–3). Despite advances in diagnosis and therapy (pharmacotherapy in particular), inadequate treatment or undertreatment of the vast majority of patients suffering from OP still remains a concern.

In CZ, where there is virtually no private health care market, conditions of drug reimbursement play a decisive role in treatment algorithms. The so-called prescription and indication restrictions are now determined for each drug individually, with regard to, among other issues, pharmaco-economic aspects of treatment. Still, there is a lack of clear information on how great parts of the public funds' costs for pharmacotherapy in OP are consumed by different groups of patients. There are also missing data quantifying drug prescription and its trends over time. Calculation of costs associated with OP in CZ was last published in 1998 (4).

* Corresponding author: e-mail: magda.vytrisalova@faf.cuni.cz; phone: 00420 495067271;fax: 00420 495067161

Considering pharmacotherapy, the major burden is represented by new costly drugs that should be strictly regulated with respect to limited public health insurance budgets. In CZ, drugs with osteoanabolic and dual effect are authorized for use in postmenopausal, male and glucocorticoid-induced osteoporosis (Table 1) but due to their reimbursement conditions, they are reserved as a second-line treatment and/or for patients with severe osteoporosis (Table 2) as well (5, 6).

Good decision practices of regulatory authorities are subject to (and depend on) targeted analyses and assessment of relevant health-economic data based both on the total cost of the disease and also

Table 1. Authorized indications of teriparatide, intact parathormone and strontium ranelate in the Czech Republic (CZ) in 2010 (13).

Drug (brand name, marketing authorization holder)	Year of marketing authorization (launch) in EU (in CZ)		Current indications
Teriparatide (Forsteo, Eli Lilly)	2003	(2005)	postmenopausal, glucocorticoid-induced and male osteoporosis
Intact parathormone (Preotact, Nycomed)	2006	(2007)	postmenopausal osteoporosis
Strontium ranelate (Protelos, Servier)	2004	(2005)	postmenopausal and male osteoporosis

Table 2. Reimbursement criteria (restrictions) of teriparatide, intact parathormone and strontium ranelate in the Czech Republic (CZ) in 2011 (13).

Drug	Prescription restrictions	Indication restrictions	
		Criteria	T-score
Teriparatide	Centres only* Indication committee approval	**Postmenopausal osteoporosis** failure of well documented antiresorptive therapy (2 years at least) + 2 vertebral fractures at least	≤ –3.0 SD (lumbar spine)
		Glucocorticoid-induced osteoporosis = 5 mg/day prednisone or equivalent for at least 6 months	≤ –2.5 SD (lumbar spine)
		Male osteoporosis failure of well documented antiresorptive therapy (2 years at least) + 2 vertebral fractures at least	≤ –3.0 SD (lumbar spine)
Intact parathormone	Centres only* Indication committee approval	Failure of well documented antiresorptive therapy (2 years at least) + 2 vertebral fractures at least	≤ –3.0 SD in lumbar spine
Strontium ranelate	Selected specialists only**	Patient should present with a) fracture, or b) contraindication of bisphosphonates or raloxifene, or c) intolerance or serious adverse effects on antiresorptives	≤ –2.5 SD (lumbar spine, proximal femur or potentially distal radius)

*12 centres in CZ are allowed to prescribe parathormones. **Physicians trained in rheumatology, orthopedics, traumatology, internal medicine, gynecology, endocrinology; treatment ≥ 2 years only if termination of bone loss is clearly demonstrated; prescription may be delegated for 1 year (prolonged only after reference assessment of the above mentioned specialist).

Table 3. Teriparatide consumption in years 2005–2011.

Year	Total number of patients (N)	Age: median (5–95% percentile)	Females (%)
2005	1	81	100.0
2006	79	73.0 (56.1–82.0)	100.0
2007	152	73.0 (55.5–82.7)	100.0
2008	237	73.6 (55.1–83.7)	96.2
2009	333	74.3 (53.5–84.3)	93.1
2010	312	70.6 (48.3–84.4)	89.8
2011	271	69.5 (39.4-85.2)	82.7

Table 4. Intact parathormone consumption in years 2005–2011.

Year	Total number of patients (N)	Age: median (5–95% percentile)	Females (%)
2009	28	76.8 (64.9–86.5)	100.0
2010	64	76.9 (64.6–87.0)	98.4
2011	77	75.4 (62.0–84.7)	97.4

*intact parathormone has been available in the Czech Republic since 2009

Table 5. Strontium ranelate consumption in years 2005–2011.

Year	Total number of patients (N)	Age: median (5–95% percentile)	Females (%)
2005	598	70.0 (53.9–82.0)	97.8
2006	2223	71.0 (53.0–83.0)	98.5
2007	3004	77.1 (60.0–89.0)	95.1
2008	3655	75.9 (59.3–88.6)	93.5
2009	4845	75.4 (57.8–88.0)	93.2
2010	5497	74.4 (57.6–87.3)	93.7
2011	5930	73.4 (56.8–86.5)	93.5

structure of the expenditures. Our ultimate goal is to calculate costs related to OP treatment. The objective of this preliminary analysis was to analyze trends in consumption of osteoanabolic (teriparatide and intact parathormone) and dual (strontium ranelate) drugs in the treatment of osteoporosis since their introduction on the market in CZ (2005–2010).

METHODS

Retrospective observational study based on prescription refills data was performed. Health insurance is compulsory under Czech law. Prescription-based database of the largest health insurance company of CZ, General Health Insurance Company of the Czech Republic (GHIC CR) that covers approximately 65% of the Czech population over 40 years, was analyzed.

An insured person with a recorded at least one package of teriparatide (TRPD), intact parathormone (iPTH) or strontium ranelate (SR) in the year of interest was defined as a patient. Time period from 2005 (launch of TRPD and SR in CZ) to 2011 was analyzed. Only anonymous population data provided directly by GHIC CR, already in an aggregated form, were analyzed, therefore, approval of the scientific ethical committee was not necessary.

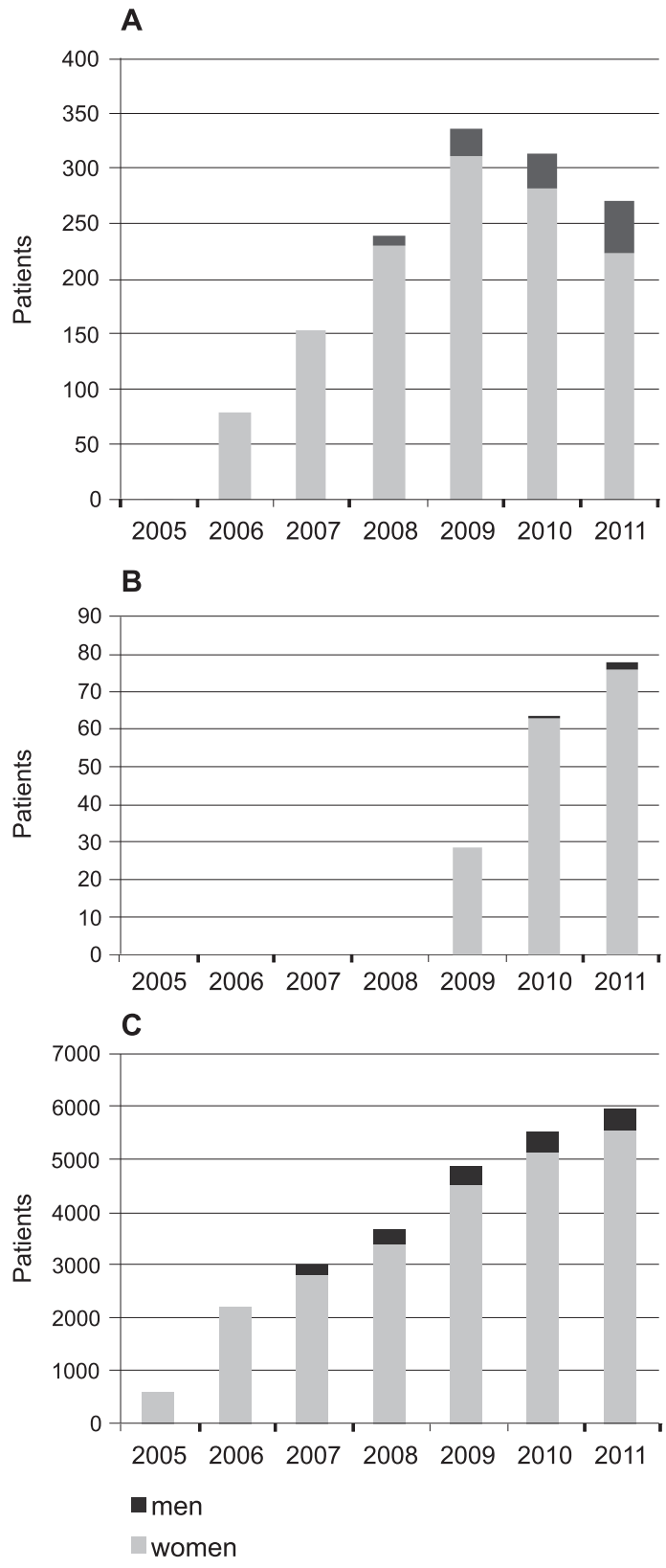

Chart 1. A – Teriparatide. B – Intact parathormone and C – Strontium ranelate consumption in General Health Insurance Company of the Czech Republic

Table 6. Osteoanabolics – cumulative consumption per patient in years 2008–2011.

	Patients (N)	Years	Monthly packages: mean (SD)
Teriparatide	351	2008-2011	16.3 (5.3)
Intact parathormone	28	2009-2011	16.5 (6.7)

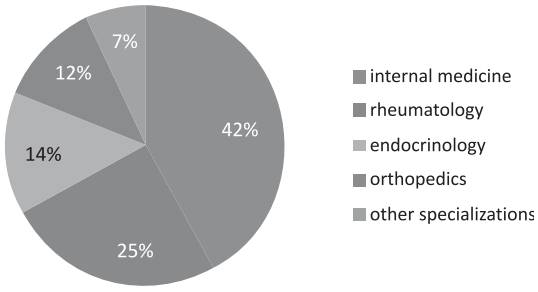

Chart 2. Specializations of doctors prescribing strontium ranelate in General Health Insurance Company of the Czech Republic (2011)

The data collected included age, gender of patient, specialization of the prescriber, time of prescription, trade name, strength and number of packages and price.

RESULTS

Since launch in CZ, the number of patients treated with osteoanabolics and SR has generally been increasing (see Tables 3–5 and Chart 1) in the observed period. The consumption of the two osteoanabolics restricted to specialized centres, however, has been relatively stable since 2009. The overall proportion of men treated with TRPD and SR increased from 2005 to 2011.

Table 6 shows the cumulative consumption per individual patient per therapy course with osteoanabolics.

Chart 2 shows the structure of specializations of physicians who prescribed SR in 2011. This structure of SR prescribers was similar during the whole observed period.

Average differences between the retail prices and reimbursement price (i.e., potential patients' co-payment) were also tracked; the highest co-payment recorded was 72 CZK (around 2.5 EUR) on a monthly package of SR in autumn 2009, which represents 6% of its retail price. For the rest of the analyzed time period all three drugs had co-payments lower or none.

DISCUSSION

The expenditures on osteoanabolic and dual drugs have been rapidly increasing since their introduction on the market in CZ. All three drugs (TRPD, iPTH, and SR) are part of the Czech OP treatment guidelines, all are reimbursed from the public health insurance funds and none of them have any other indications besides OP. There has also been no competition on the market in terms of generic or biosimilar drugs. The present population analysis of OP drug consumption is among the first in CZ.

The increasing trend of osteoanabolics (TRPD and iPTH) consumption seems to reach a plateau in 2009 (consumption rate in 2010 similar to that in 2009). Also an increase in the proportion of men treated with TRPD and SR has been observed. This is in line with the extension of indications for these two drugs and reflects greater emphasis placed on male OP in the last years. Increasing numbers of male patients were found also in our previous study that evaluated bisphosphonate consumption in 2002–2006 (7).

In accordance with the reimbursement criteria, namely "prescription restrictions", outpatient internists, followed by rheumatologists, endocrinologists and orthopedic surgeons contributed most significantly to the prescription of SR. Osteoanabolics (TRPD and iPTH), drugs administered parenterally, are very expensive treatment options; their single daily dose is on average 10 times more expensive than SR. Osteoanabolics also may be prescribed only in specialized centers (12 selected osteocenters in CZ). These aspects probably account for the fact that their use is not very widespread and their consumption reached the plateau relatively soon.

In our previous study we identified that annually around 40 thousand patients of GHIC CR (e.g., 40.397 in 2005) were treated with oral bisphosphonates alendronate and risedronate indicated only for OP. As much as 98% of the patients were women (7). Confronting this with the estimates on the overall OP Czech population of 400,000 women (adjusted to the GHIC CR market share of 65% in CZ) led

us to the estimate that only around 15% of potential OP patients (women) are treated with bisphosphonates in CZ. However, according to the national guideline, the first line intervention is calcium and cholecalciferol supplementation, which is available and reimbursed without any prescription conditions. Considering the three osteoanabolic and dual drugs (iPTH, TRPD, and SR) analyzed in the present study, their indication criteria position them in the next therapeutic line clearly after bisphosphonates (and raloxifen): they are indicated (and reimbursed) in case of contraindication, well-documented intolerance or treatment failure (development of osteoporotic fracture in the course of treatment) of antiresorptives. Therefore, it is not unexpected that the observed patient numbers for SR, iPTH and TRPD are significantly lower compared to the previously mentioned bisphosphonates. Even though SR has not appeared to reach its consumption peak yet, in 2011 (the highest number so far) around 6 thousand patients were treated, which is a mere 2% of the overall estimate on OP female population. Given the patient numbers of the two specialized centers only-resctricted osteoanabolics (TRPD and iPTH), their relative proportion in the overall OP treatment is even much lower than that of SR.

The two osteoanabolics (TRPD and iPTH) have a specific: unlike most, if not all, other drugs used in chronic conditions such as OP, these drugs have clearly stated the length of the therapy in their Summaries of Product Characteristics (SmPC): it is 24 months in both cases. This defined period, originally 18 months (until February 2009), is not as restrictive in the case of SmPC of parathormone as in that of teriparatide. Nevertheless, this therapy length for both drugs is naturally reflected also in the official Czech OP treatment guidelines (5, 6). The health insurance accounting in CZ does not enforce specifying the precise date of treatment administration by the providers; however, both drugs were charged for a monthly package in a regular interval for each patient. Detailed analysis (not shown) revealed that the cumulative accounting (i.e., a number of monthly packages) clearly corresponds and agrees well with the duration of treatment. Currently, we are not aware of any other study evaluating the real-world therapy length. Our data showing the average over 16 monthly packages per individual therapy course suggest the therapy is either shorter or less intensive than according to the SmPCs. The reasons could be the non-adherence (non-compliance) of the physician to the SmPC and guideline, and the non-adherence of the patient to the treatment schedule. Also responsible may be for instance patient's acute new or exacerbated comorbidity that precludes further OP treatment either due to its seriousness (such as life-threatening disease or event) or due to the appearance of new contraindications for the ongoing OP treatment making it to be stopped. Also the real-world tolerability of the drugs certainly may play a role in shortening the treatment course from the optimal as described in the guidelines and SmPCs. Therefore, our finding should be interpreted with caution as the underlying reasons may be multiple and we do not have data on their relative importance. Certainly, it is a topic for longer follow-up and further research.

A potential barrier in access to a new drug could be a significant co-payment paid by patients which makes the drug less attractive. However, this is not the case for any of the three drugs, as they (TRPD, iPTH and SR) have been virtually fully reimbursed already since their launch on the market in CZ. Another barrier, which is common for all new original drugs, may be prescription budget limits placed upon the physicians by the insurance companies. This "limit" essentially means that within each specialization, any single physician's spending (on prescription drugs separately) is benchmarked within a period (year) with all other doctors, as well as his/her spending is compared with the same doctor's spending in different years. Then, those physicians spending overly (often due to prescribing new expensive drugs) are penalized. These mechanisms are complex and regulated by many factors, starting from Czech Ministry of Health's annual decrees, which reflect the economic situation of the health care insurance budgets, and ending in the individual financial contracts between doctors and health insurance companies. Even though these budget restrictions are certainly important and worth mentioning in OP treatment, their deeper analysis, due to their complexity, individuality and irregularity in the long term, extends beyond the scope of our study.

The age of patients treated with TRPD and SR was stable in the observed period (median 71–74 years). In comparison, a study carried out in Slovak population showed that treatment with SR or bisphosphonates was most frequently started in 72 years-aged patients in 2009 (8). In our analysis, we analyzed the consumption of SR from its very introduction onto the market in CZ. In the first year, when all the patients were newly treated with SR, their median age was 70 years. In the following years it increased a little, but the data suggest that the treatment with SR is started at a similar age as in the Slovak population, i.e., in the patient's early seventies. The Slovak analysis reported the age when

treatment was started, studied only female population and calculated data for SR together with bisphosphonates. These facts make precise and valid comparisons impossible.

GHIC CR currently manages health insurance for more than 60% of the insured people (65% in people over 40 years) in CZ and has a major impact on drug policy as well as pricing and reimbursement of various health services including new medical technologies (9). At present, GHIC CR introduces the principles of pharmacoeconomics and health technology assessment into evaluation of medical devices and together with the Ministry of Health (Prague) and the State Institute for Drug Control (Prague) into the assessment and appraisal of pharmaceuticals. The database is considered to be precise, because the data originate in pharmacies claiming drug reimbursement, which is a process regularly audited. Patients can be dispensed their prescribed medicine in any pharmacy in CZ. The data from this database are valid for the pharmacoepidemiological research (10).

Population studies using prescription-based databases have several well-known limitations such as changing of health insurer and medication not captured in the database (11, 12), however, these aspects do not seem relevant to our pilot analysis as switching health insurer is negligible in the higher-age population and also due to the origin of the data in pharmacies being economically interested in reporting their claims completely and precisely to the insurance fund. Also analyzing only part of the population insured by a single company may lead to some bias depending namely on the age and illness structure of the group. However, this may not be the case here, because of the large market share of GHIC CR representing around 60% of the Czech population, and even more in the higher age group with OP concerned in the present study. The relative share of patients according to their age and their gender in GHIC CR has been stable over the years. GHIC CR also has contracts with virtually all health care providers including all specialized centers. Therefore, we believe that the analyzed population is a good representative sample of the overall OP population and their pharmacological treatment, which can be safely extrapolated to virtually all Czech population.

In conclusion, the consumption of osteoanabolic and dual drugs has been rapidly increasing during 2005-2011. Prescribing of expensive osteoanabolic drugs in selected centers based on Indication committee approval is probably well regulated in the last years to avoid extensive consumption growth. Consumption of SR, which is prescribed by specialist doctors with no ties to the approval process, has a tendency to a permanent increase. Consumption rates in men have been increasing but remain still relatively low. Subsequent updated analysis of consumption of other osteoporosis drugs (antiresorptives in particular), along with the calculation of the relevant treatment costs should be undertaken to provide a further, more detailed and economic insight into current OP management.

Acknowledgments

We gratefully acknowledge cooperation and quantitative data provision by General Health Insurance Company of the Czech Republic. The project was supported by grant GAUK No. 103107/c/2007/FaF from the Charles University Grant Agency and research project SVV 267 005.

REFERENCES

1. Štepán J., Záhora R., Poláková L.: Cas. Lek. Cesk. 137, 237 (1998).
2. Stepan J., Vaculik J., Pavelka K. et al.: Calcif. Tissue Int. 90, 365 (2012).
3. Skála-Rosenbaum J., Bartoníček J., Říha D. et al.: Int. Orthop. 35, 587 (2011).
4. Štěpán J., Šmíd M., Prokeš M. et al.: Cas. Lek. Cesk. 137, 707 (1998).
5. Bayer M., Jeníček J., Kučerová I. et al.: http://www.smos.cz/docs/dp_smos1.pdf
6. Bayer M., Jeníček J., Kučerová I. et al.: http://www.smos.cz/docs/dp_smos2.pdf
7. Vytřísalová M., Blažková Š., Palička V., Štěpán J.: Osteol. Bull. 14, 139 (2009).
8. Bielik J., Jureček L., Hroncová D.: Farmakoekonomika a liekova politika 6, 25–28 (2010).
9. General Health Insurance Company of the Czech Republic. Annual report 2011, http://www.vzp.cz/en/annual-reports.php 20.11. 2012.
10. Kucera Z., Vlcek J., Hejdova M.: Pharmacoepidemiol. Drug Saf. 14, 61 (2005).
11. Dezii C.M.: Manag. Care 10, 42 (2001).
12. Seeman E., Compston J., Adachi J. et al.: Osteoporos. Int. 18, 711 (2007).
13. State Institute for Drug Control: http://www.sukl.eu/modules/medication/search.php; 20. 11. 2012.

Received: 02. 05. 2013