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Bone 162 (2022) 116477

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Dispensing anti-osteoporotic drugs changed during the COVID-19 pandemic

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ARTICLE INFO

Keywords:
COVID-19
Anti-osteoporotic therapy
Lockdown
Osteoporosis
Autoregressive integrated moving average models
Dispensing
Austria

ABSTRACT

Objectives: Caring for osteoporosis patients has proven challenging during the COVID-19 pandemic due to repeated lockdowns in Austria. The distinct possibility of insufficient treatment regimens is therefore a matter of pressing concern. The aim of the study was to assess alterations in dispensing anti-osteoporotic drugs during the COVID-19 pandemic.

Patients/methods: This study was a nationwide retrospective register-based observational study which included all patients in Austria aged ≥50 who received at least one prescription for anti-osteoporotic medication between January 2016 and November 2020. Pseudonymised individual-level patients' data were obtained from social insurance authorities. Anti-osteoporotic agents were divided into: (i) oral bisphosphonates, (ii) intravenous bisphosphonates, (iii) selective estrogen receptor modulators (SERMs), (iv) teriparatide (TPTD) and (v) denosumab (DMAB). We used interrupted time series analysis with autoregressive integrated moving average models (ARIMA) to predict drug dispensing.

Results: There were 2,884,374 dispensations of anti-osteoporotic drugs to 224,598 patients between 2016 and 2020. The mean monthly prescriptions for oral bisphosphonates (−14.5 %) and SERMs (−12.9 %) decreased during the COVID-19 pandemic when compared to the non-COVID-19 period. Dispensing for intravenous bisphosphonates (1.7 %) and teriparatide (9.5 %) increased. Prescriptions for DMAB decreased during the first lock-down, however increased by 29.1 % for the total observation time.

The Arima models showed that in March 2020 (beginning of the 1st COVID-19 lockdown), there was a decrease of 778 dispensings, with a further increase of 14 dispensings every month for denosumab; a decrease by 178 dispensings, with a further increase of 23 dispensings every month for zolendronic acid; a decrease by 2950 dispensings, but with a further increase of 236 dispensings every other month for ibandronate and a decrease by 1443 dispensing with a further decrease of 29 dispensings for alendronate than predicted, had the lockdown not occurred.

Conclusions: The total number of prescriptions dispensed to patients treated with anti-osteoporotic medications declined rapidly during first COVID-19 lockdown. The observed decrease of DMAB during the first lockdown rebounded in the following months. Considering the massive treatment gap for osteoporosis, and the related fracture risk, clinicians should continue treatment, even during a pandemic.

1. Introduction

Care for osteoporosis patients during the COVID-19 pandemic is challenging. Due to lockdowns and various restrictions, the management of osteoporosis has necessarily changed. An IOF-NOF-ESCEO global survey reported an increase in telemedicine consultation during the COVID-19 pandemic [1]. DXA scans were delayed and treatment decisions were mainly based on clinical risk factors, rather

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https://doi.org/10.1016/j.bone.2022.116477
Received 8 April 2022; Received in revised form 27 May 2022; Accepted 25 June 2022
Available online 29 June 2022

than on bone mineral density measurements [1,2]. Fracture risk calculation by FRAX also decreased during the pandemic. A 50 % reduction of FRAX sessions was observed in most European countries [3]. Moreover, outpatient units were temporarily shuttered, FLS services ceased, and virtual fracture liaison clinics were established [4].

Due to these extenuating circumstances, diagnosis of osteoporosis is complex in pandemic situations and might also influence initiation and continuation of anti-osteoporotic therapy. More than 40 % of clinicians worldwide reported difficulties in arranging appropriate osteoporosis medications during the COVID-19 crisis [1]. Around 20 % of respondents reported delays in providing intravenous or subcutaneous medication.

The discontinuation of denosumab (DMAB) is associated with high bone turnover and risk for multiple vertebral fractures [5,6]. Based on the joint guidance on COVID-19 vaccination and osteoporosis management, DMAB should not be delayed >7 months after the last injection [7]. However, it has been shown, that adherence to DMAB was lower during the COVID-19 lockdown than beforehand [8]. We recently reported a decrease in prescriptions of anti-osteoporotic drugs during March and April 2020 when the first lockdown took place in Austria due to the COVID-19 pandemic [9]. A 22 % and 23 % decrease of DMAB prescriptions compared to the six months prior was observed during the first lockdown. Moreover, we found a decrease in prescriptions for intravenous zoledronic acid and ibandronate prescriptions. We did not quantify how many dispensings were not prescribed due to lockdown. In the present study, we aimed to forecast the monthly utilisation of anti-osteoporotic drugs had a lockdown not taken place.

To our knowledge this is the first study which specifically examines changes in dispensing of anti-osteoporotic drugs associated with the COVID-19 pandemic and compare observed dispensings against predicted ones. We hypothesised that anti-osteoporotic drug prescriptions decreased at the beginning and during the lockdown in March 2020.

2. Material and methods

2.1. Study setting

The healthcare system in Austria consists of hospital-based inpatient and outpatient units located at hospitals and >900 independent outpatient clinics as well as private practices of doctors, half of whom are contracted to the health insurance funds [10]. The diagnosis of osteoporosis, initiation of treatment and ongoing prescription of specific medication is provided by general practitioners, specialists for internal medicine, orthopaedics, gynaecology or physical medicine. According to the current reimbursement scheme of pharmaceuticals, the prescription of drugs can be made directly or after seeking approval by doctors of the insurance company after double checking the indication. Prescribed drugs can only be sold in pharmacies in Austria. The study comprises all dispensed anti-osteoporotic medications by pharmacies in Austria between January 1, 2016, and November 31, 2020.

2.2. COVID-19 and restrictions in Austria

The incidence of infections with the novel coronavirus (COVID-19) increased up to 12.1 per 100,000 persons on March 16, 2020 [11] when the first governmental lockdown in Austria started to halt the spread of the virus. The lockdown was implemented between March 16, 2020, and May 1, 2020, with stepwise abrogation of restrictions from April 14, 2020, onwards. The initial restrictions included avoidance of public places, reduction of social contacts, travelling, closing of schools and universities, restaurants and shops, except for basic services and groceries. Only five exceptions were proposed: i) to avert immediate danger of life, limb or property, ii) assistance and care of vulnerable persons, iii) work if home office is not possible, iv) exercise outdoors alone and with people living in the same household/pets. On November 3rd, 2020, a "light" version of the lockdown went into effect. It introduced a curfew and the closing of restaurants, leisure facilities and museums. Since this "light" lockdown was unable to slow down the numbers of reported new infections, the federal government announced that the restrictions would be tightened again and a "hard" lockdown from November 17, 2020, until December 7, 2020, followed. Outpatient clinics and private practices reduced their availability or closed to reduce patient visits and establish prevention concepts. Direct access to health care facilities was therefore limited. Despite that, the possibility for electronic prescriptions was released and non-uniform strategies like telephone contacts were established by the clinics. Pharmacies remained generally opened.

2.3. Study population

The study was a nationwide retrospective register-based observational study. Pseudonymised individual-level patients' data were obtained from social insurance authorities and the Federal Ministry of Labour, Social Affairs, Health, and Consumer Protection in Austria.

We analysed data for all patients in Austria ≥50 years of age who were prescribed anti-osteoporotic drugs between January 1, 2016, and November 31, 2020. Patients receiving strontium ranelate were excluded from analysis.

For patients on parathyroid hormone therapy (n = 19) we did not calculate predictions due to low numbers and the probability of indications other than osteoporosis. The study flowchart is presented in Fig. 1.

2.4. Outcomes

We included the following anti-osteoporotic medications: alendronate (Anatomic Therapeutic Chemical code M05BA04), risedronate (M05BA07), ibandronate (M05BA06), zolendronic acid (M05BA08), denosumab (M05BX04), raloxifene (G03XC01), teriparatide (H05AA02).

Anti-osteoporotic agents were divided into: (i) oral bisphosphonates (comprising alendronate and risedronate), (ii) intravenous bisphosphonates (comprising ibandronate and zolendronic), (iii) selective estrogen receptor modulators (SERMs) (raloxifene), (iv) teriparatide (TPTD) and (v) denosumab (DMAB). The strengths and preparations for the indication of bone metastasis were excluded: oral ibandronate 50 mg, intravenous ibandronate 6 mg, intravenous zolendronic acid 4 mg, subcutaneous denosumab 120 mg.

2.5. Statistical analysis

We first calculated the percentage change in the mean number of prescriptions prior to and during the COVID-19 pandemic (i.e., mean number of dispensings in March 2020 through November 2020 were divided by mean number of dispensings in January 2016 through February 2020 and multiplied by 100). We plotted dispensings for oral and intravenous bisphosphonates, teriparatide, SERMs and denosumab as bar charts. "COVID-19 pandemic" was defined as the period between March 2020 and November 2020, "pre-COVID-19" as the period between January 2016 and February 2020 and "first lockdown" as March and April 2020.

In a second step, we used time series forecasting based on monthly purchases of anti-osteoporotic medications between January 1, 2016, and November 31, 2020. March 2020 was set as a step variable (representing a time point before and after lockdown).

We used interrupted time series analysis with autoregressive integrated moving average models (ARIMA). We followed the analytical approach presented by Schaffer and colleagues [12]. We first plotted time series data for each drug and checked the ACF/PACF plots of undifferenced data. We observed that datasets were non-stationary and autocorrelated and continued with data differencing. We plotted and checked differenced/seasonally differenced data. Next, we created step

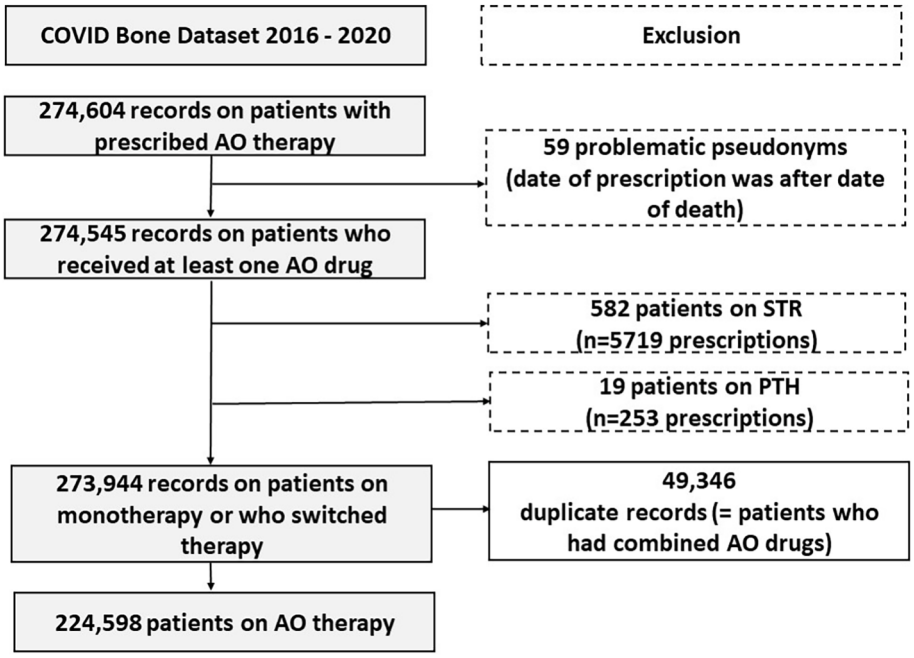

Fig. 1. Study design. STR, strontium ranelate; AO, anti-osteoporotic.

and ramp variables, representing step change and change in slope, respectively. We used *auto.arima* function to identify the best fitting ARIMA model based on minimising the information criteria. We checked residuals of the final models.

Statistical analyses were conducted in IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY, USA) and in R version 3.5.2 [13]. Percentage change in dispensings was executed with MS Excel (Microsoft, 2019).

2.6. Ethics review

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the City of Vienna (Approval number: EK 21-046-VK).

3. Results

There were 2,884,374 dispensings of anti-osteoporotic drugs to 224,598 patients between 01/2016 and 11/2020. There were 196,772 women (87.6 %, mean age 75.0, SD 10.2) and 27,826 men (12.4 %, mean age 73.9, SD 10.6). Prescriptions patterns and frequency of prescriptions per patient per medication is provided in Table 1.

The mean monthly prescriptions for oral bisphosphonates decreased during the COVID-19 pandemic from 23,797 to 20,342 (−14.5 %), compared to the pre-COVID-19 period. Dispensings of intravenous bisphosphonates were in total relatively stable with 18,796 dispensings during the COVID-19 pandemic compared to 18,491 dispensings prior to COVID (+1.6 %).

This is mainly explained by the fact that dispensings of ibandronic acid raised from 17,880 to 18,228 (+2.0 %). However, dispensings for zoledronic acid decreased from 611 to 560 (−7.1 %) during the COVID pandemic. We further observed a decrease in dispensings of SERMs from 1180 pre-COVID-19 to 1028 during the COVID-19 pandemic (−12.9 %). Dispensings of teriparatide agents increased during the COVID-19 pandemic from 1024 to 1121 (+9.5 %).

Although a significant decline in prescriptions for DMAB was observed during the lockdown in March and April 2020 (−24 %), the dispensing increased by 29.1 % for the total observation time (Fig. 2).

Forecasting models showed that the total number of prescriptions dispensed to patients treated with anti-osteoporotic medications declined rapidly in March 2020 and April 2020 with a subsequent compensation in the following months. The largest drops in absolute terms were observed for ibandronate, followed by alendronate, denosumab, zolendronic acid and risedronate. For ibandronate, we observed that the lockdown in March 2020 was associated with a decrease of 2950 dispensings, but with a further increase of 236 dispensings every other month. For denosumab, there was a decrease of 778 dispensings, with a further increase of 14 dispensings every month. For zolendronic acid, there was a decrease of 178 dispensings, with a further increase of 23 dispensings every month. For risedronate, there was a decrease of 144 dispensings, with a further decrease of 23 dispensings every month.

The estimated changes are displayed in Table 2. For the ease of interpretation of step change and change in slope, we provide an example for alendronate. For alendronate, the estimated step change

Table 1
Prescription patterns of selected anti-osteoporotic drugs between January 2016 and November 2020 in adult population aged ≥50 years old.

		Frequency of prescriptions per patient					
Drug	ATC code	One-time	Two-times	Three-times	Four-times	Total number of patients on therapy	Total number of prescriptions
Alendronate	M05BA04	13,992	4928	3066	2287	54,105	1,094,352
Risedronate	M05BA07	3168	1020	716	481	15,354	278,564
Ibandronate	M05BA06	17,265	8340	6233	6022	104,027	1,058,024
Zolendronic acid	M05BA08	5704	3039	2810	1883	14,106	35,688
Denosumab	M05BX04	8916	5766	5213	5185	32,012	288,202
Raloxifene	G03XC01	480	182	127	101	2539	68,273
Teriparatide	H05AA02	524	273	223	199	2455	61,271

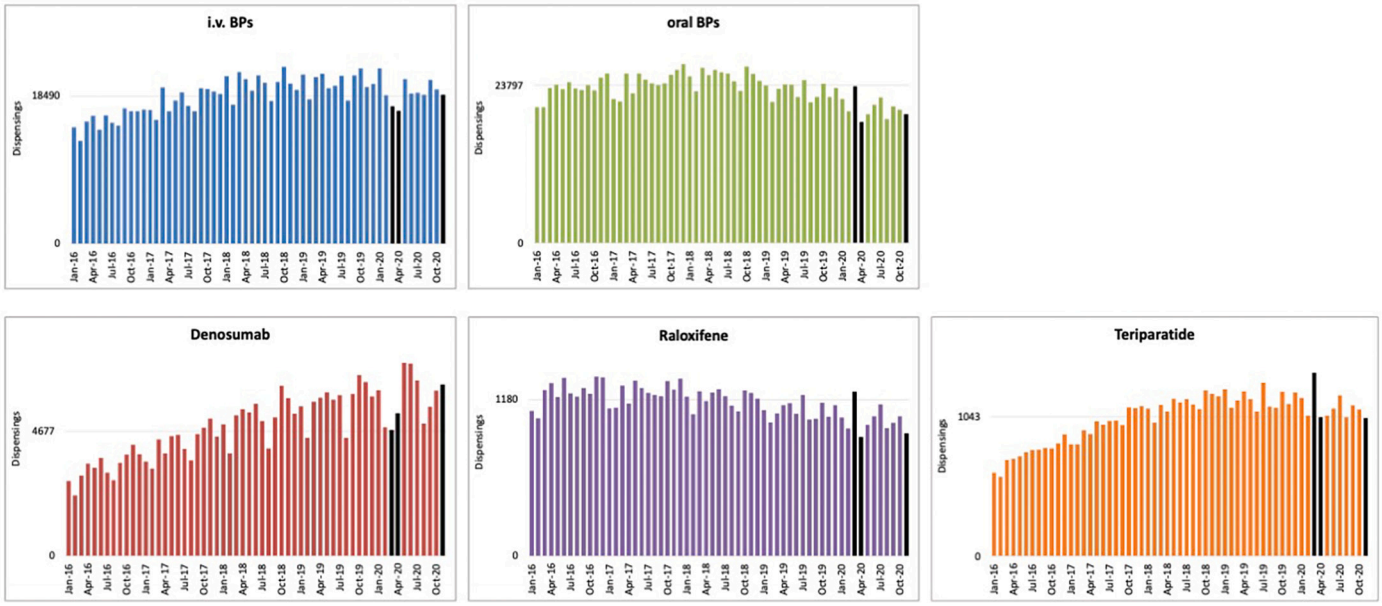

Fig. 2. Drug dispensing from January 2016 till November 2020. Black bars indicate COVID-19 lockdowns. Thin lines and numbers on Y-axis indicate absolute number of dispensed anti-osteoporotic drugs prior the COVID-19 pandemic. i.v., intravenous; BPs, bisphosphonates.

Table 2
Changes in anti-osteoporotic dispensings in Austria after first lockdown in March 2020 during COVID-19 pandemic based on ARIMA models.

	Estimated change (95 % CI)	Change in slope (95 % CI)
Alendronate	−1443 (−2870; −17)	−29 (−327; 270)
Risedronate	−144 (−650; 362)	−23 (−114; 68)
Ibandronate	−2950 (−4222; −1678)	236 (−9; 481)
Zolendronic acid	−178 (−331; −26)	23 (−6; 51)
Denosumab	−778 (−1625; 68)	14 (−120; 148)
Raloxifene	5 (−63; 73)	−5 (−17; 6)
Teriparatide	27 (−59; 114)	−13 (−31; 5)

was minus 1443 dispensings (95 % CI −2870 to −17), while the estimated change in slope was minus 29 dispensings per month (95 % CI −327 to 270). This means that COVID-19 restrictions in March 2020 were associated with a decrease of 1443 dispensings, with a further decrease of 29 dispensings every month. In other words, there were 1472 (1443 + 29) fewer dispensings in March 2020 than predicted had the lockdown not occurred. Fig. 3 shows the values predicted by our ARIMA models without lockdown compared with the observed values.

4. Discussion

In this nationwide study we observed serious declines in dispensings of anti-osteoporotic drugs during the COVID-19 lockdown in March 2020 with a compensation in the following months. For almost all assessed anti-osteoporotic medications, apart from raloxifene and teriparatide, the predicted values for dispensing in March 2020 were lower than dispensed.

Our findings are consistent with the hypothesis that during the lockdown the dispensing of anti-osteoporotic medications decreased mainly due to restrictions associated with the lockdown rather than by shortages in delivery of certain drugs to pharmacies. Based on the Austrian Federal Office for Safety in Health Care, no distribution restrictions for anti-osteoporotic drugs were reported in 2020 (personal communication). Based on a report from the United States, almost 41 % of adults avoided or delayed medical care due to concerns about COVID-19, including > 31 % of patients who avoided routine care appointments [14].

There is currently no evidence for increased risk for COVID-19 infection or worsening of disease in patients on anti-osteoporotic therapy [15]. Patients on oral bisphosphonates were not associated with increased risk of COVID-19 infection, hospitalisation, or intensive care [16]. Women above 50 years old on Denosumab did not seem to be in higher risk of COVID-19 infections either [17]. A similar outcome regarding hospitalisation, ICU admission and mortality risk was found for infected women on bisphosphonate, denosumab, or teriparatide therapy and those without treatment [18]. The authors suggest that anti-osteoporotic drugs should therefore not be discontinued during COVID-19 infection [18]. This suggestion is in line with the more recent data showing that oral bisphosphonates and vitamin D were not associated with an increased risk for COVID-19 infections [19]. Denosumab, zolendronic acid, and calcium had a rather positive effect for relative risk for COVID-19 infections [19]. Based on a Joint Guidance on Osteoporosis management in the era of COVID-19 from the ASBMR, AACE, Endocrine Society, ECTS and NOF, patients who already taking osteoporosis medications should continue to receive ongoing medications, oral or intravenous agents [32]. At the same time, caution should be taken for usage of estrogen and raloxifene, as they may modestly increase thrombotic risk; and COVID-19 patients may be in increased risk for hypercoagulable complications [33,34]. Anti-osteoporotic drugs do not seem to attenuate COVID-19 vaccination either. However, due to common side effects, known as flu-like-symptoms, likely mimicking a COVID-19 infection, intravenous bisphosphonates should be administered in a 4–7-day interval. Due to injection site reactions, DMAB and romosozumab should also be given in a 4–7-day interval. Oral bisphosphonates and teriparatide do not have to be discontinued [15,30]. On the other hand, current treatment regimens for patients hospitalized with COVID-19 might have an effect on bone health. The current recommendations of the Panel on the COVID-19 by National Institute of Health [35] recommends using dexamethasone in hospitalized patients with COVID-19 who require mechanical ventilation. The anti-inflammatory effects of corticosteroids mitigate the inflammatory response against COVID-19, and the use of corticosteroids have been associated with improved outcomes in patients with critical COVID-19. Osteoporosis and increased fracture risk are well-known comorbidities of prolonged ang high cumulative glucocorticoids doses. The evidence on effect of antiviral therapies against COVID-19 on bone is lacking. However, it is clear that long hospitalization and immobilization

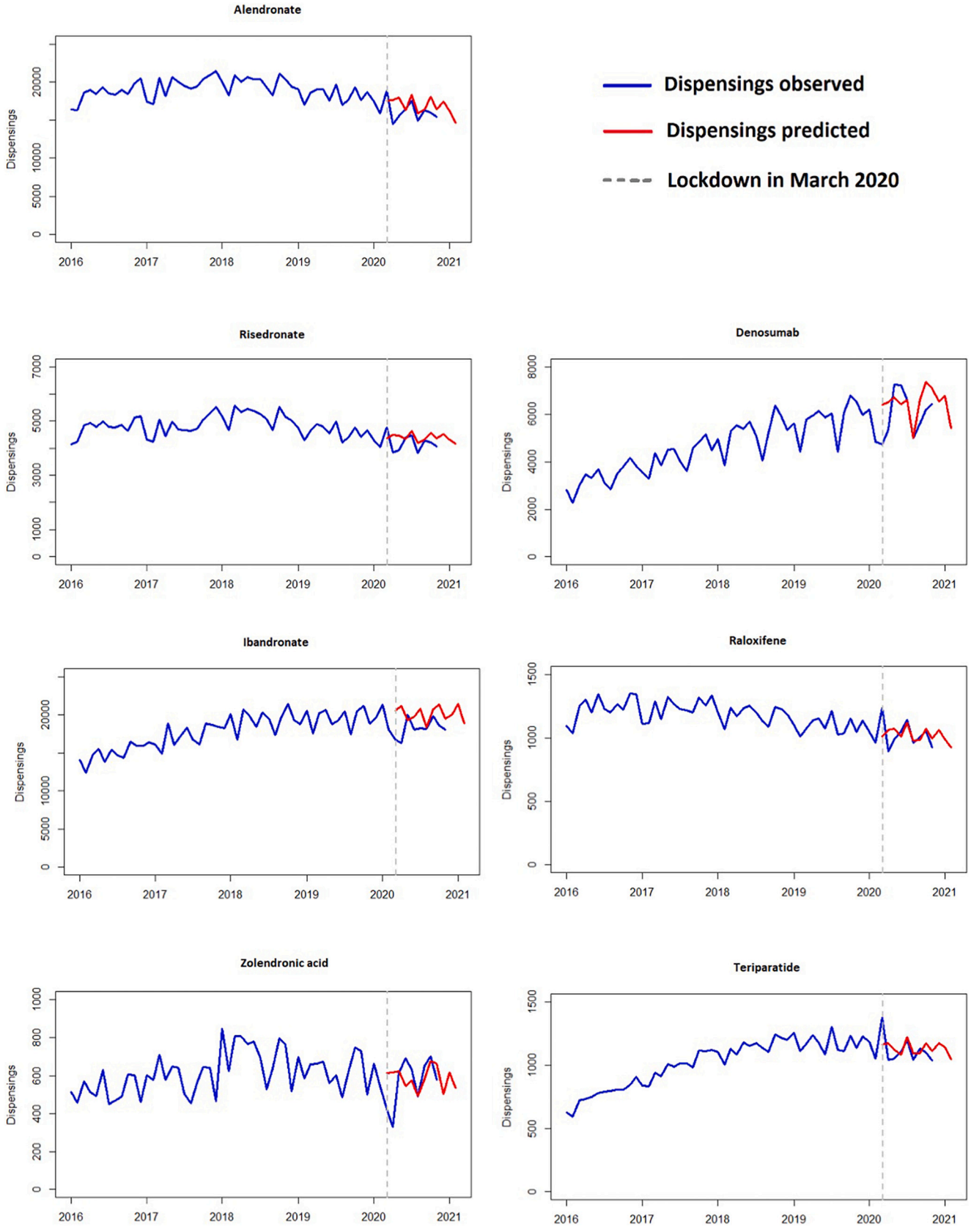

Fig. 3. Predictions by ARIMA models without lockdown compared with the observed values.

negatively impact the bone and muscle strength and leads to increased risk of falls and fractures. With regard to vitamin D there is insufficient evidence to recommend either or against the use of it for the prevention or treatment of COVID 19.

The shift toward higher rates in teriparatide observed in our study were more likely caused by market authorisation of three generic forms in Austria introduced in January 2020 (Terrosa®, Gedeon Richter), February 2020 (Movymia®, Stada) and October 2020 (Teriparatid, Ratiopharm). The prescription of teriparatide became easier for medical doctors and the generic forms of teriparatide cheaper than before, probably leading to the observed increase in dispensings.

We further observed increases of dispensings every month after March 2020 until November 2020 for ibandronate, zolendronic acid and denosumab. We interpret this as a compensation dispensing for a lockdown month.

Difficulties in the administration of anti-osteoporotic drugs, especially a delay of denosumab and zoledronic acid application, have been reported in the survey by the National Osteoporosis Foundation [20]. Similarly, a recent study from Singapore has shown that adherence to denosumab was significantly lower during the COVID-19 lockdown than prior to lockdown [8]. A decline of both, diagnostic procedures and therapeutic interventions has been observed worldwide. A survey by the National Osteoporosis Foundation revealed that in-patient appointments were available only for a minority of patients during the first lockdowns [20]. A forty percent reduction in diagnosis of osteoporosis during COVID-19 was reported by Sisó-Almirall et al. [21]. In Dubai, geriatric in-patient services, including care of osteoporosis patients, declined by 70 % and the average number of DXA scans per month declined by 58.4 % [22]. Consequently screening and diagnosis of osteoporosis did not take place and patient visits were partly supplemented by telemedicine [22]. Education programmes and self-administration, especially of denosumab, as well as telemedicine appointments has been suggested as a valuable new tool for patient care [23,24].

Drug dispensing also decreased for drugs used for the treatment of chronic diseases in children during the COVID-19 pandemic [25]. A decrease of treatment was observed for other musculoskeletal diseases as well. A decline of primary and revision total joint arthroplasties of knee and hip during the COVID-19 pandemic was reported [26].

The initiation and continuation of anti-osteoporotic treatment during the COVID-19 pandemic was repeatedly recommended by the National Osteoporosis Foundation. Osteoporosis patients should not delay initiation or continuation of treatment [27]. Oral bisphosphonates may be favourable in pandemic situations compared to parenteral agents [28]. Current guidelines recommend a transition to oral bisphosphonates if intravenous bisphosphonates are delayed >9 months. For osteoanabolic agents teriparatide and romosozumab, treatment should be continued and an interruption of >3 months should be avoided. Failing this, a switch to oral bisphosphonates should be considered [29]. A delay of intravenous bisphosphonates for several months is possible, since efficacy on bone mineral density, bone turnover markers and fracture protection remain. This contrasts with denosumab, where application should not exceed 7 months. Then, a switch to oral bisphosphonates is recommended. Teriparatide treatment should generally be continued. A delay of maximum 3 months is possible. In case of romosozumab, treatment should not be delayed longer than 2–3 months [30].

This study has several strengths. First, we report the most recent national data on dispensing of anti-osteoporotic drugs, which captures dispensings administered by public pharmacies or primary care apothecaries. Second, we showed detailed timely dispensings per patient from January 2016 to November 2020. Third, we used ARIMA modelling to estimate the changes in anti-osteoporotic drugs dispensing, adjusting for autocorrelation and seasonality. In this study we calculated, besides ARIMA estimates, relative differences in mean dispensing between two time periods (03/2020 – 11/2020 and 01/2016 – 02/2020), which is relatively easy and frequently used method to observe differences, though without any adjustments. With this method we observed relative increase in dispensing of ibandronate and decrease of zoledronate, whereas with ARIMA method a decrease due to lockdown for both these drugs was shown. Therefore, we suggest for future studies to use rather robust methods when assessing differences between time periods than a method on relative differences. Our study limitations include a lack of information on indication for prescribing. For example, Zoledronat 4 mg is usually used once monthly for the treatment of bone metastasis, hypercalcemia in case of malignancy as well as multiple myeloma. Administration of Zoledronat 4 mg was set as an exclusion criterion in data extraction. However, we cannot fully rule out the use of Zoledronat 4 mg also for osteoporosis in few cases. Yet, for osteoporosis treatment, only Zoledronat 5 mg is approved in Austria and were therefore analyzed. rhPTH (1–84) is available for the treatment of chronic hypoparathyroidism. However, also teriparatide might be used for the treatment of hypoparathyroidism and sometimes for fracture healing (both off-label). Other limitations is, that our study analyzed only dispensing of medications but not their consumption. Lastly, our data did not contain medications administered in hospitals.

5. Conclusion

Management of osteoporosis during the COVID-pandemic presents new challenges. We observed a decline in dispensing of parenteral and oral anti-osteoporotic drugs in Austria during the first COVID-19 lockdown in March 2020 in Austria with compensation dispensings in the following months. Any decrease in prescription rates is worrying and the overall trend should be to treat the growing number of patients with osteoporosis. Taking into account the massive treatment gap for osteoporosis [31] and the related fracture risk, clinicians should continue treatment even in times of pandemics. Healthcare systems should invest more financial and structural effort into telemedicine to mitigate the impact of the current COVID-19 crisis and to be prepared for other sudden global events.

CRediT authorship contribution statement

RK and TS initiated the study concept and design and performed the part of the analysis. MB performed the analysis and interpretation of data. RK, MB, JH drafted the manuscript. TS, HR, JZ contributed to interpretation of data and co-wrote the manuscript. BR contributed to data acquisition. All authors read and approved the final manuscript.

Declaration of competing interest

The authors state no conflict of interest regarding this manuscript.

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