Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Review

Genetic factors influencing the efficiency of alendronate therapy in postmenopausal women with primary osteoporosis

[1,2]Alina D. Ciubean, [1,2]Laszlo Irsay, [1,2] Rodica A. Ungur, [1,2]Viorela M. Ciortea, [1,2]Ileana M. Borda, [1,2]Gabriela B. Dogaru, [1,2]Ioan Onac, [3]Adrian P. Trifa, [3]Cristian M. Voina, [4]Stefan C. Vesa, [4]Anca D. Buzoianu

[1]Department of Rehabilitation Medicine, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2]Department of Rehabilitation, Clinical Rehabilitation Hospital, Cluj Napoca, Romania; [3]Department of Medical Genetics, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [4] Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Abstract. Osteoporosis is a common skeletal disease characterized by low bone mineral density and microstructural deterioration of bone tissue, which increases the risk of fragility fractures. Several drugs are available for the treatment of osteoporosis. Among them, alendronate, belonging to the amino-bisphosphonate family, is widely used. The therapeutic response to antiosteoporotic therapy is variable, ranging from 70 to 75%, based on changes in bone mineral density. Studies have been conducted to search for an explanation for this variation, especially in the pharmacogenetics field. Multiple single nucleotide polymorphism were evaluated regarding treatment response to alendronate based on baseline characteristics, biochemical markers of bone turnover, bone mineral density and genotype in postmenopausal women with primary osteoporosis from different ethnic groups. The most promising results seems to be those reported in genes of the mevalonate and Wnt pathway, as their components (e.g. FDPS, SOST, LRP5 etc.) have been shown to have a certain impact in mediating treatment response to alendronate in different populations.

Key Words: osteoporosis, alendronate, genetic polymorphism, bone turnover markers, pharmacogenetics.

Corresponding Author: L. Irsay, e-mail: laszloirsay@gmail.com

Introduction

Osteoporosis (OP) is a common skeletal disease characterized by low bone mineral density (BMD) and microstructural deterioration of bone tissue, which increases the risk of fragility fractures (Ralston 2010).

Bone is a living tissue that is constantly renewed through a process called 'bone remodeling', which consists of a resorption phase (removal of old bone by osteoclasts) and a formation phase (replacing the resorbed tissue by osteoblasts). This process is controlled by complex genetic, hormonal, nutritional and environmental factors. When bone resorption exceeds bone formation, microarchitectural changes occur, bone strength is compromised and the risk of fracture increases (Riancho & Hernández 2012). BMD is an important predictor of fractures and it is also used as a diagnostic standard for OP (Boudin et al 2016).

Fracture prevention is the most important clinical goal of OP therapy, as they are a major cause of morbidity in the population (Sebba 2008). Common fracture sites related to bone fragility are those of the hip (proximal femur), proximal humerus, distal radius and the vertebral bodies. Hip fractures cause acute pain and loss of function, and nearly always require inpatient care. Also, more importantly, recovery is mainly slow and rehabilitation is often incomplete, resulting in a huge social and economic burden. Vertebral fractures may cause acute pain and loss of function and they often recur, however, and the consequent disability increases with their number. Distal radial fractures also lead to acute pain and loss of function, but functional recovery is usually good or excellent (Kanis et al 2019; López-Delgado et al 2016).

To date, several drugs are available for the treatment of OP. Among them, amino-bisphosphonates (N-BPs) have a potent anti-osteoclastic effect that results in an inhibition of bone resorption, increased bone mass and decreased risk of both vertebral and peripheral fractures. Furthermore, it is important to highlight that N-BPs may prevent apoptosis in osteoblasts by a cell survival mechanism through extracellular signal-regulated kinases that affects the production of bone mass (Riancho et al 2012).

Alendronate (ALN), a potent and specific inhibitor of osteoclast-mediated bone resorption belonging to the N-BP family, is widely used in Europe, America and Asia (Ogawa & Ouchi 2012). ALN acts by inhibition of the farnesyl pyrophosphate synthase in osteoclasts, of which the nitrogen moiety makes it more affinitive with bone mass (Tsoumpra et al 2015).

Studies have demonstrated that treatment ALN increases BMD and decreases the risk of vertebral fractures by 50% and the risk of peripheral fractures (e.g. hip, radius) by 20–30%. Although the therapeutic use of ALN is effective, the expected response to antiosteoporotic therapy seems to be variable, ranging from 70 to 75% of cases, based on changes in BMD. Approximately 8–25% of patients had a change in lumbar spine BMD less or equal to 0% after 2 years treatment of ALN, risedronate or ibandronate (Nguyen & Eisman 2006; Cummings et al 1998; Quandt et al 2005; Bonnick et al 2007; Crilly et al 2000). Several studies have been conducted to search for an explanation for this variation based on baseline characteristics, early changes in biochemical markers of bone turnover and early changes in BMD. In patients treated with N-BPs, the early decrease in bone turnover is related to the long-term increase in BMD (Briot & Roux 2005). Also, the effects of N-BPs on

Table 1. Association between genetic polymorphisms and treatment response to alendronate based of bone mineral density

Study	Year	Gene	Polymorphism	n	Ethnicity	Results	p-value
Palomba et al.	2003	VDR	*rs1544410 (BsmI)*	68	Italian	*bb genotype*: higher increase in spine BMD	<0.01
Creatsa et al.	2011	VDR	*rs1544410 (BsmI)*	42	Greek	*BB* genotype: less increase in spine BMD	0.054
Conti et al.	2015	VDR	*rs1544410 (BsmI)*	150	Italian	No significant association	0.97
			rs2228570	150	Italian	TT genotype: higher increase in BMD	<0.047
Zheng et al.	2016	OPG	10 SNPs (data not shown)	501	Chinese	No significant association	>0.05
		RANKL	4 SNPs (data not shown)				
		RANK	16 SNPs (data not shown)				
Wang et al.	2009	OPG	A163G	67	Chinese	Genotype AA: higher increase in hip BMD	0.014
			T245G			Genotype TT: higher increase in hip BMD	0.046
Wang et al.	2014	MVK	*rs10161126*	500	Han Chinese	G allele: higher increase in spine BMD	0.002
			rs4766613			No significant association	0.05
			rs11067376				
		PMVK	*rs4578216*				
		GGPS1	2 SNPs (data not shown)				
		FDFT1	10 SNPs (data not shown)				
		IDI2	4 SNPs (data not shown)				
		MVD	2 SNPs (data not shown)				
		FDPS	rs11264359				
Zhou et al.	2015	SOST	*rs1234612*	545	Chinese	TT: less increase in spine BMD TC: higher increase in spine BMD	0.018
			rs865429	545	Chinese	CC genotype: less increase in hip BMD	0.009
Zhou et al.	2014	LRP5	*rs3736228* (A1330V)	607	Chinese	C allele: higher increase in spine BMD TT genotype: less increase in spine BMD	0
Wang et al.	2016	DKK1	*rs2241529*	639	Chinese	AA genotype: less increase in total hip BMD	0.016
			4 SNPs (data not shown)			No significant association	>0.05
Marini et al.	2008	FDPS	*rs2297480*	234	Danish	CC genotype: less increase in BMD	0.6
Choi et al.	2009	FPDS	3 SNPs (data not shown)	144	Korean	No significant association	>0.05
		GGPS1	2 SNPs (data not shown)				
Olmos et al.	2012	FDPS	*rs2297480*	1186	Spanish	AA genotype: higher increase in BMD	0.001
			rs11264359			AA genotype: higher increase in BMD	0.001
			rs17367421			No significant association	0.6
Liu et al.	2013	FDPS	*rs2297480*	639	Chinese	No significant association	>0.05
Arko et al.	2002	ERβ	*RsaI*	79	Slovenian	No significant association	0.09
Han et al.	2016	GGPPS	6 SNPs (data not shown)	540	Chinese	No significant association	>0.05
Lima et al.	2017	IL17A	*rs7747909*	69	Brazilian	No significant association	>0.05
		IL23R	*rs10889677*			No significant association	>0.05
		IL12B	*rs3212227*			TT genotype: higher increase in BMD	0.058
		INF-γ	*rs2069705*			GG genotype: higher increase in BMD	0.016

SNP=Single Nucleotide Polymorphism; n=number of participants; BMD=bone mineral density

the mevalonate pathway can explain not only their molecular mechanism of action, but also the different potency of the various amino-bisphosphonate compounds. But the main focus is towards genetic factors, believed to influence the response to antiosteoporotic drugs in terms of BMD and bone turnover markers (Russell et al 2008; Ferlazzo et a 2006).

In the last decades, researchers have turned their attention towards new areas of interest, pharmacogenetics and pharmacogenomics, starting from the premises that response to therapeutic agents is influenced by an individual's underlying genotype, which could explain the different responses that are commonly observed in clinical practice (e.g. good, moderate or no response). Knowledge of a person's genotype could allow tailoring drug treatments and target those most likely to benefit and have less adverse effects. Given the high prevalence of OP, it would be desirable to have pharmacogenetic data allowing to tailor drug therapy to patient's characteristics. This would increase the chances of obtaining a good treatment response (e.g. increase bone strength and reduce fracture risk), while also maybe limiting the possibility of adverse effects (Gennari et al

Table 2. Association between genetic polymorphisms and treatment response to alendronate based on bone turnover markers

Study	Year	Gene	n	Ethnicity	Bone turnover markers	Results	p-value
Palomba et al.	2003	VDR	68	Italian	*OC*	bb genotype *(rs1544410)*: lower serum levels after treatment	<0.01
					DPD		
					Ca		
					P1NP		
Creatsa et al.	2011	VDR	42	Greek	*OC*	No significant association before or after treatment	>0.05
					CTX		
					25-OH-VIT D		
Conti et al.	2015	VDR	150	Italian	*Ca*	No significant association before or after treatment	>0.05
					ALP		
Zhou et al.	2015	SOST	545	Chinese	*CTX*	AA genotype (*rs851054*): higher serum levels at baseline	<0.05
					25-OH-VIT D	No significant association before or after treatment	>0.05
Zhou et al.	2014	LRP5	607	Chinese	*CTX*	CC and CT genotypes (*rs3736228*): lower serum levels after treatment	0
					ALP	CC and CT genotypes (*rs3736228*): lower serum levels after treatment	0
Wang et al.	2016	DKK1	639	Chinese	*ALP*	No significant association before or after treatment	>0.05
					CTX	Correlation with *rs1528877* and *rs2241529* at baseline	<0.05
Marini et al.	2008	FDPS	234	Danish	*CTX*	CC genotype (*rs2297480*): lower serum levels after treatment	0.049
					OC	No significant association before or after treatment	>0.05
Liu et al.	2013	FDPS	639	Chinese	*Ca*	No significant association before or after treatment	>0.05
					Phosphate	No significant association before or after treatment	>0.05
					ALP	CC genotype (*rs2297480*): lower serum levels after treatment	<0.05
					CTX	No significant association before or after treatment	>0.05
Arko et al.	2002	ERβ	79	Slovenian	*OC*	No significant association before or after treatment	>0.05
					DPD		
Han et al.	2016	GGPPS	540	Chinese	*Ca*	No significant association before or after treatment	>0.05
					Phosphate	No significant association before or after treatment	>0.05
					ALP	No significant association before or after treatment	>0.05
					CTX	TT genotype of *rs10925503*: higher serum levels	0.012
					25-OH-VIT D	No significant association before or after treatment	>0.05
Lima et al.	2017	IL17A	69	Brazilian	*ALP*	Correlation with INF-γ -1616 genotypes (GG/AA) at baseline	< 0.0001
		IL23R			*Ca*	Correlation with IL23R +2284 genotypes (CC/CA) after treatment	0.016
		IL12B			*PTH*	Correlation with INF-γ -1616 genotypes (AA/GA) at baseline	0.017
		INF-γ			*25-OH-VIT D*	Correlation with IL17A +672 genotypes (GG/GA) and IL12B +1188 genotypes (TT/TG) after treatment	<0.05

OC=osteocalcin; DPD=urinary deoxypyridinoline; Ca=total calcium; P1NP=procollagen type 1 amino-terminal propetide; CTX=C-telopeptide; 25-OH-Vit D=25-hydroxyvitamin D; ALP= alkaline phosphatase; PTH=parathyroid hormone

2002; Liu et al 2006; Marini & Brandi 2009; Marini & Brandi 2012; Marini & Brandi 2013).

As an individual's response to drugs is under the control of genes, genetic profiles could help clinicians predict individual drug response and prescribe the right drug and dose, thereby optimizing efficacy and lowering risk of adverse effects. The objective of personalized medicine is to create a crossover bridge from the traditional 'one-drug-fits-all' to genotype-based individualized therapies (Marini & Brandi 2014).

In the last decades, a handful of OP candidate genes have been investigated with regard to response to antifracture agents such as ALN. The main studies are reviewed below and their main characteristics are outlined in Table 1 and Table 2.

Discussion

Today, it is well established the fact that genetic factors account for approximately 15-30% of personal drug response and for up to 95% for drug effects. The genetics of OP comprises two main areas: genetics of disease susceptibility and pharmacogenetics of drug response. While the former has been widely studied, the latter still requires much more information and research, as the results are inconclusive.

Pharmacogenetics has an important role in the field of personalized medicine. It represents the intersection of pharmacology and genetics, with a focus on correlating DNA polymorphisms and/or gene expression with a drug's efficacy or toxicity. The major goal is to develop specific genetic tests to identify „good responders" and patients at risk for developing adverse reactions. Currently, application of pharmacogenetics into clinical practice is limited to a few drugs, and the genetic prediction of drug response is far from clear for many complex diseases. When talking about chronic disorders, such as metabolic bone diseases like OP, that require long-term drug therapy, it is important to choose the most effective and risk-free pharmacological agent. If common polymorphisms in the candidate genes for OP modify the effects of ALN on BMD or bone turnover markers, identifying and characterizing them might help physicians assess the pharmacogenetic profile of ALN therapy and could lead to a new understanding about bisphosphonate action and its regulation of bone metabolism.

Multiple studies have been conducted on genes, single nucleotide polymorphisms (SNPs) and pathways of interest to search for an explanation for this variation in treatment response based on baseline characteristics, early changes in biochemical markers of bone turnover and early changes in bone mineral density. One of the first gene considered in relation with the genetics of osteoporosis is vitamin D receptor gene (VDR). Vitamin D is a steroid hormone that plays an important role in calcium homeostasis and bone metabolism, and VDR gene mediates normal bone mineralization and remodeling (Kochupillai 2008). Since Morrison et al (1994) reported a relationship between the VDR gene and BMD, discordant studies have been published and it is still not clear whether VDR genotypes influence bone mass accretion and/or postmenopausal bone loss (Uitterlinden et al 2006; Moran et al 2015; Mohammadi et al 2014). Palomba et al (2003) analyzed an association between *rs1544410* SNP of VDR gene and response to ALN after 12 months of treatment in 68 postmenopausal Caucasian women, showing that the TT genotype has a better response in terms of BMD than CC genotype ($p< 0.01$) and that serum and urinary levels of bone turnover markers also decreased significantly more, while heterozygous CT showed an intermediate response that was not significantly different. Creatsa et al (2011) also investigated the possible VDR *rs1544410* genotype-alendronate treatment interaction. Patients with the CC genotype had lower lumbar spine BMD ($P = 0.054$) and T-score ($P = 0.030$) versus subjects with at least one T allele (CT or TT).In terms of bone turnover markers, total calcium (Ca), serum osteocalcin (OC), procollagen type 1 amino-terminal propetide (P1NP), 25-hydroxyvitamin D (25-OH-VIT D) and serum C-telopeptide (CTX) were evaluated before and after ALN treatment, but no significant association was found between genotypes. Interestingly, Conti et al (2015) showed that therapeutic response was independent of *rs1544410* genotypes in 150 patients treated with ALN for 3 years. The same author (Conti et al 2015) found association between treatment response to ALN and another polymorphism of the VDR gene, *rs2228570* (C/T). The homozygous TT carriers showed a marked improvement in term of delta t-score (calculated as the difference between the t-score after three years of treatment and the t-score at baseline) than both heterozygous TC and homozygous CC (both $p < 0.0001$). Furthermore, no difference between Ca and alkaline phosphatase (ALP) values before and after treatment was observed. Even though studies show discordant results, CC genotype of *rs1544410* SNP in the VDR gene was found to have lower BMD values and an unsatisfactory response to ALN, making it a SNP that should be considered as a possible factor influencing the efficacy of the anti-osteoporotic treatments, but further research is needed in the area.

As mediators of estrogen action, the genes encoding ERα and ERβ have been considered important candidates for the determination of osteoporotic risk (Gennari et al 2005). The association of *rs1256049* polymorphism in the Erβ gene and response to ALN treatment was evaluated by Arko et al (2002), but showed no statistically significant correlation between genotypes and changes in lumbar spine or femoral neck BMD, serum OC and urinary deoxypyridinoline (DPD) after 1 year of ALN therapy, only a trend towards lower increase in lumbar spine BMD of heterozygous patients ($p = 0.099$). It is well-established that estrogen deficiency plays an important role in the pathogenesis of postmenopausal osteoporosis (Rapuri et al 2006), but their implication in treatment response to ALN and other N-BPs is not well known. It is unclear whether their involvement is mainly important in patients treated with hormone therapy, as most studies in the field showed, or their implications are wider.

The osteoprotegerin (OPG)/receptor activator of nuclear factor-kappaB (RANK)/RANK ligand (RANKL) system is an additional mechanism correlated to both bone resorption and bone formation. Normally, osteoblasts express RANKL, which interacts with RANK that induces osteoclast differentiation and proliferation. As a control mechanism, osteoblasts also secrete OPG, which binds to RANKL and prevents osteoclast activation. Given this data, several studies have suggested that polymorphic variants in the RANKL, RANK, and OPG genes may influence bone density and bone turnover (Hsu et al 2006; Kim et al 2007). Wang et al (2009) analyzed 2 SNPs in the OPG gene (A163G and T245G) in 67 postmenopausal Chinese women undergoing ALN treatment for 1 year, showing that at site A163G,

the percentage of hip BMD increase was higher in genotype AA of A163G (p=0.014) and in genotype TT for T245G (p=0.046). Recently, Zheng et al (2016) evaluated 40 SNP's in the OPG, RANKL, and RANK genes in relation to treatment response to ALN. Although the *rs7239261* polymorphism of the RANK gene was significantly associated with baseline L1–L4 BMD (p=0.0004) and that patients with an A allele (C/A and A/A) of the same polymorphism had a higher baseline L1–L4 BMD than did patients with the C/C genotype, no association was observed between any SNP and BMD change or treatment response to 1 year of alendronate therapy in 501 postmenopausal Chinese women with osteoporosis or osteopenia.

Despite the interesting results regarding VDR, ERα, Erβ or OPG/RANK/RANKL, none of the above-mentioned studies have investigated the molecular targets of N-BPs. In fact, neither of them can be directly associated with the N-BPs molecular mechanism of action, and how could they modulate treatment response to N-BPs are still unknown.

Dickkopf WNT Signaling Pathway Inhibitor 1 (DKK1), a protein coding gene and an inhibitor of Wnt pathway by interacting with low density lipoprotein receptor-related protein 5/6 (LRP5/6), modulates bone formation and leads to decreased osteoblast number, decreased bone formation rate, and lower serum OC levels (Yao et al 2011; Cheng et al 2011). In a cohort of 60 postmenopausal women, DKK1 was increased in the serum of patients with reduced BMD (Wagner et al 2011). Thus, DKK1 has been an attractive therapeutic target for osteoporosis. In recent years, polymorphisms of DKK1 have been found to correlate to BMD and fracture risks (Ahmed et al 2013). Five SNP's of *DKK1* gene were analyzed in 639 Chinese postmenopausal women with osteoporosis or osteopenia. After 12 months of ALN treatment, only *rs2241529* polymorphisms of *DKK1* significantly correlated to percentage changes in total hip BMD (p=0.040). Participants with AA genotype had less increase in total hip BMD than women with AG genotype (p=0.016). No correlation was found between the other SNPs of *DKK1* and bone response to ALN treatment. As for biochemical markers of bone turnover, only serum CTX correlated at baseline with 2 SNPs, *rs1528877* and *rs2241529*, respectively (p<0.05) (Wang et al 2016).

Sclerostin, an osteocyte-derived inhibitor of osteoblast activity, antagonizes Wnt signaling in both osteocytes and osteoblasts by binding to the lipoprotein receptor-related protein (LRP5/6) coreceptor (Canalis 2013; Ke et al 2012). Sclerostin is encoded by SOST gene. Loss-of-function mutations of SOST lead to rare genetic skeletal disorders such as sclerosteosis and Van Buchem disease, associating with a high BMD phenotype and low risk of fractures (Lewiecki 2014). Zhou et al (2015) correlated polymorphisms in the SOST gene for the first time to responsiveness in terms of BMD to ALN treatment in 545 Chinese postmenopausal women. After 12 months of treatment, genotypes at *rs1234612* locus were associated with percentage change of lumbar spine BMD (p=0.015). Participants with homozygous common alleles had less increase in lumbar spine BMD than those with heterozygous genotypes (p=0.018). Genotypes at *rs865429* locus were associated with percentage changes in femoral neck BMD after 12 months of treatment (p=0.030), while homozygous minor alleles had less increase. He concluded that changes of lumbar spine BMD were correlated to *rs1234612* and changes of femoral neck BMD were correlated to *rs865429*. In terms of bone markers, genotypes at only *rs1513670* locus were associated with percentage changes in serum ALP levels (p = 0.005) after 3 months of treatment. Genotypes at the other SNPs loci were uncorrelated to percentage change of ALP or CTX after treatment.

LRP5 (low-density lipoprotein receptor-related protein 5) is the most important membrane receptor of the Wnt signaling pathway and it was reported as a candidate gene for susceptibility to osteoporosis and also in response to risedronate treatment in men (Kruk et al 2009). Loss-of-function mutations of LRP5 lead to osteoporosis-pseudoglioma syndrome, whereas activating mutations are responsible for autosomal dominant inherited disorders characterized by high bone mass (Balemans et al 2007). Zhou et al (2014) investigated the association between *rs3736228* polymorphism of the LRP5 gene in 576 postmenopausal women. Even though they did not find an association between this polymorphism and BMD, serum levels of ALP and CTX at baseline, final results show that the presence of the C allele led to a larger increase in lumbar spine BMD after 6 and 12 months of treatment. Also, women that are T homozygotes may have a poor response to ALN treatment. As for markers of bone resorption and formation, participants with CC and CT genotypes had a larger decrease of serum CTX and ALP levels than women with TT genotype after ALN treatment (both p = 0.000). One of the most important signaling pathways in bone is Wnt, as it is crucial in differentiation and proliferation of bone cells, making its components (e.g. SOST, LRP5 and DKK1) worthy of being studied in regard to OP and treatment response to antiosteoporotic agents. For all the SNPs studied regarding their involvement in treatment response to ALN, interesting results have emerged, but only relevant to the Chinese population. Knowing that there could be different allelic or genotypic distribution in Caucasians compared to Asian populations, and there is no data published so far, it is important to test these hypotheses in other ethnic groups.

Farnesyl diphosphate synthase (FDPS) is a key enzyme of the mevalonate pathway and the main target for N-BPs, thus allelic variants of the FDPS gene could be associated with response to ALN treatment. Because FDPS is inhibited by all the N-BPs, the antiresorptive potency of various N-BPsseems to correlate with their ability to inhibit FDPS (Venegas et al 2010; Ferlazzo et al 2006). Marini et al (2008) analyzed the correlation between *rs2297480* polymorphism in the FDPS gene and response to ALN in 234 Danish postmenopausal women. Results show that spine and femur BMD increases was lower in patients with CC genotype compared to AC and AA genotype, but it did not reach statistical significance (p=0.60), suggesting that the presence of the A allele could predict a better treatment response to ALN. In a study of 144 Korean women, Choi et al. (2009) did not find an association of two SNP's in the FDPS gene (*rs2297480* and *rs11264361*) with BMD response after 12 months of bisphosphonate therapy. However, Olmos et al. (2012) showed a significant association between *rs2297480* alleles and hip BMD changes induced by N-BS's. Women with AA genotype gained 1% per year of BMD, and women with CC genotype lost about 1.6%. Also, the *rs11264359* polymorphism in the FDPS gene showed similar trends. Interestingly, Liu et al. (2013) showed no significant difference in BMD at lumbar spine among different

genotypes of FDPS in 639 postmenopausal Chinese women after 12 months of ALN treatment. As for biochemical markers, CC genotype of *rs2297480* had lower serum levels of ALP after treatment.

Also, more recently, Wang et al (2014) showed that genotypes of *rs11264359* polymorphism in the FDPS gene have no significant association with treatment response to ALN in terms of BMD. The same group of authors (Wang et al 2014) analyzed 23 SNP's in 7 genes that encode key enzymes of the mevalonate pathway as candidates to explain the variable responses in BMD to ALN treatment in 500 postmenopausal Han Chinese women. He concluded that one SNP, *rs10161126* in MVK (mevalonate kinase) gene, is significantly associated with BMD response at L1–L4 (p=0.002) and that the G allele of *rs10161126* could be a genetic factor positively associated with being a responder in terms of BMD at the lumbar spine.

GGPS1 (geranylgeranyl pyrophosphate synthase) is another important target of N-BPs in osteoclasts, which belongs to the trans-prenyltransferase family. ALN inhibits GGPS1 in the mevalonate pathway, which is why genetic variance of GGPS1 gene is speculated to affect the skeletal response to ALN (Dudakovic et al 2008; Chen et al 2013). In a recent study on 540 Chinese women, BMD at the lumbar spine and femoral neck had no obvious difference among all genotypes of GGPS1 gene after ALN treatment. Of the six SNP's analyzed, TT genotype of *rs10925503* polymorphism had significantly higher serum CTX level than those with TC or CC genotype, but no significant differences in percentage changes of serum ALP and CTX levels were found after 12 months of ALN treatment (Han et al 2016). Given the fact that the mevalonate pathway is the main target for N-BPs, it is a perfect place to start the search for candidate genes involved in treatment response to this pharmacological agent. Results of the studies conducted so far, although they require confirmation in larger populations, suggest the possible use of pharmacogenetic screening in the choice of ALN as an antiosteoporotic agent.

It is presumed that there are also other pathways that could influence BPs therapeutic response, particularly the immune related ones. Among them, cytokines and their network are known to display several essential functions in the bone remodeling and are closely related to OP treatment (Yuan et al 2012; Talaat et al 2015). Recently, cytokines such as IFN-γ have been described as inhibitor of RANK/RANKL/OPG pathway through TRAF 6 protein degradation and IL-17 as inducer of RANK-L and Th17 cells production, both affecting bone homeostasis processes (Talaat et al 2015; Guerrini & Takayanagi 2014). In a recent study, Lima et al (2017) analyzed 4 SNPs in the IL23R, IL17A, IL12B and IFN-γ genes and their relation with treatment response in 69 postmenopausal women from Northeast Brazil treated over a period of 1–4 years with BPs (77% of patients used alendronate, followed by risendronate-16% and ibandronate-7%). Results show that only the INF-γ -1616 polymorphism exhibited association regarding BMD changes. The GG genotype was associated with increased BMD values in FN area (GG/AA, p = 0.016) and decreased BMD values in TH area (GG/GA, p = 0.019; GG/AA, p = 0.011) after 3 and 4 years of treatment. Additionally, IL12B +1188 T/T genotype showed a trend of association (TT/TG; p = 0.058), with increased BMD values in TH area after 1 year of treatment. Among the other SNPs, no significant differences were observed. As for biochemical markers, IL17A +672 G/A and IL12B +1188 T/G genotypes were associated with higher vitamin D levels. Even though the immune pathways are believed to have an important part in bone metabolism, more research is needed in this area.

Results from pharmacogenetic studies seem to suggest that patient genotyping could be useful to target osteoporosis drug treatments to subjects most likely to respond in terms of BMD and bone turnover marker variation. However, most of these studies have used a candidate gene approach and included small numbers of patients and very few of them have been replicated in two or more independent cohorts. Also, due to some limitations, such as inadequate sample size or sampling errors, genetic differences between different ethnic groups and the complexity of human genome, at the moment no definite gene variations have been conclusively shown to be responsible for the regulation of any anti-osteoporotic drug response.

The application of specific genetic tests to identify subjects most likely to respond well and not to develop adverse reactions before the beginning of drug treatment is important mostly for chronic diseases, such as OP, that require long-term pharmacological treatment. Also, pharmacogenetics could help map new molecular drug targets, moving from 'one drug fits all' to personalized therapy. Certainly, the genes to be evaluated should be those encoding drug targets, drug metabolizing enzymes and drug transporters.

Conclusion

In conclusion, pharmacogenetic association studies need to be extended and confirmed in larger cohorts, in different ethnic groups and/or in multicentric studies. The field of pharmacogenetics still requires much more information and research, as the results are inconclusive. In the future, pharmacogenetic tests, prior to initiating a certain drug, especially for a chronic disease like OP, could optimize the pharmacological therapy to have maximum efficacy and minimal adverse effects.. The results of the studies described above are promising, as they show the potential use of pharmacogenetic tests to tailor decisions about the prescription of ALN in women with OP. The most promising genes that could predict treatment response to ALN seem to be mainly those involved in the mevalonate or Wnt pathway.

References

Ahmed SF, Fouda N, Abbas AA. Serum Dickkopf-1 Level in Postmenopausal Females: Correlation with Bone Mineral Density and Serum Biochemical Markers. J Osteoporos 2013;2013:460210. doi: 10.1155/2013/460210

Arko B, Preželj J, Komel R, Kocijančič A, Marc J. No major effect of estrogen receptor beta gene RsaI polymorphism on bone mineral density and response to alendronate therapy in postmenopausal osteoporosis. J Steroid Biochem Mol Biol 2002;81(2),147-152. doi: 10.1016/S0960-0760(02)00061-4

Balemans W, Devogelaer JP, Cleiren E, Piters E, Caussin E, Van Hul W. Novel LRP5 missense mutation in a patient with a high bone mass phenotype results in decreased DKK1-mediated inhibition of Wnt signaling. J Bone Miner Res 2007;22(5),708-716. doi: 10.1359/jbmr.070211

Bonnick S, Saag KG, Kiel DP, McClung M, Hochberg M, Burnett SAM, et al. Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years. J Clin Endocrinol Metab 2006;91(7),2631-2637. doi: 10.1210/jc.2005-2602

Boudin E, Fijalkowski I, Hendrickx G, Van Hul W. Genetic control of bone mass. Mol Cell Endocrinol 2016;432,3-13. doi: 10.1016/j.mce.2015.12.021

Briot K, Roux C. What is the role of DXA, QUS and bone markers in fracture prediction, treatment allocation and monitoring?. Best Practice & Research Clinical Rheumatology 2005;19(6):951-64. doi: 10.1016/j.berh.2005.06.004

Canalis E. Wnt signalling in osteoporosis: Mechanisms and novel therapeutic approaches. Nature Reviews Endocrinology 2013;9(10):575-583. doi: 10.1038/nrendo.2013.154

Chen SH, Lin SW, Lin SR, Liang PH, Yang JM. Moiety-linkage map reveals selective nonbisphosphonate inhibitors of human geranylgeranyl diphosphate synthase. J Chem Inf Model 2013;53(9):2299-2311. doi: 10.1021/ci400227r

Cheng Z, Biechele T, Wei Z, Morrone S, Moon RT, Wang L, et al. Crystal structures of the extracellular domain of LRP6 and its complex with DKK1. Nat Struct Mol Biol 2011;18(11):1204-1210. doi: 10.1038/nsmb.2139

Choi HJ, Choi JY, Cho SW, Kang D, Han KO, Kim SW, et al. Genetic polymorphism of geranylgeranyl diphosphate synthase (GGSP1) predicts bone density response to bisphosphonate therapy in Korean women. Yonsei Med J 2010;51(2):231-238. doi: 10.3349/ymj.2010.51.2.231

Conti V, Russomanno G, Corbi G, Toro G, Simeon V, Filippelli W, et al. A polymorphism at the translation start site of the vitamin D receptor gene is associated with the response to anti-osteoporotic therapy in postmenopausal women from Southern Italy. Int J Mol Sci 2015;16(3):5452-5466. doi: 10.3390/ijms16035452

Creatsa M, Pliatsika P, Kaparos G, Antoniou A, Armeni E, Tsakonas E, et al. The effect of vitamin D receptor BsmI genotype on the response to osteoporosis treatment in postmenopausal women: A pilot study. J Obstet Gynaecol Res 2011;37(10):1415-1422. doi: 10.1111/j.1447-0756.2011.01557.x

Crilly RG, Sebaldt RJ, Hodsman AB, Adachi JD, Brown JP, Goldsmith CH, et al. Predicting subsequent bone density response to intermittent cyclical therapy with etidronate from initial density response in patients with osteoporosis. Osteoporos Int 2000;11(7):607-14. doi: 10.1007/s001980070082

Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. Jama 1998;280(24):2077-82.

Dudakovic A, Wiemer AJ, Lamb KM, Vonnahme LA, Dietz SE, Hohl RJ. Inhibition of Geranylgeranyl Diphosphate Synthase Induces Apoptosis through Multiple Mechanisms and Displays Synergy with Inhibition of Other Isoprenoid Biosynthetic Enzymes. J Pharmacol Exp Ther 2007;324(3):1028-1036. doi: 10.1124/jpet.107.132217

Ferlazzo V, Sferrazza C, Caccamo N, Di Fede G, Di Lorenzo G, D'Asaro M, et al. In vitro effects of aminobisphosphonates on Vγ9Vδ2 T cell activation and differentiation. Int J Immunopathol Pharmacol 2006;;19(2):309-17. doi: 10.1177/039463200601900208

Gennari L, Merlotti D, De Paola V, Calabrò A, Becherini L, Martini G, et al. Estrogen receptor gene polymorphisms and the genetics of osteoporosis: A HuGE review. American Journal of Epidemiology 2005;161(4):307-20. doi: 10.1093/aje/kwi055

Gennari L, Becherini L, Falchetti A, Masi L, Massart F, Brandi ML. Genetics of osteoporosis: Role of steroid hormone receptor gene polymorphisms. Journal of Steroid Biochemistry and Molecular Biology 2002;81(1):1-24. doi: 10.1016/S0960-0760(02)00043-2

Guerrini MM, Takayanagi H. The immune system, bone and RANKL. Archives of Biochemistry and Biophysics 2014;561:118-23. doi: 10.1016/j.abb.2014.06.003

Han L wen, Ma D dou, Xu X jie, Lü F, Liu Y, Xia W bo, et al. Association Between Geranylgeranyl Pyrophosphate Synthase Gene Polymorphisms and Bone Phenotypes and Response to Alendronate Treatment in Chinese Osteoporotic Women. Chinese Med Sci J 2016;31(1):8-16. doi: 10.1016/S1001-9294(16)30016-5

Hsu YH, Niu T, Terwedow HA, Xu X, Feng Y, Li Z, et al. Variation in genes involved in the RANKL/RANK/OPG bone remodeling pathway are associated with bone mineral density at different skeletal sites in men. Hum Genet 2006;118(5):568-577. doi: 10.1007/s00439-005-0062-4

Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2019;24(1):23-57. doi: 10.1007/s00198-018-4704-5

Ke HZ, Richards WG, Li X, Ominsky MS. Sclerostin and dickkopf-1 as therapeutic targets in bone diseases. Endocrine Reviews 2012;33(5):747-783. doi: 10.1210/er.2011-1060

Kim JG, Kim JH, Kim JY, Ku SY, Jee BC, Suh CS, et al. Association between osteoprotegerin (OPG), receptor activator of nuclear factor-κB (RANK), and RANK ligand (RANKL) gene polymorphisms and circulating OPG, soluble RANKL levels, and bone mineral density in Korean postmenopausal women. Menopause 2007;14(5):913-918. doi: 10.1097/gme.0b013e31802d976f

Kochupillai N. The physiology of vitamin D: Current concepts. Indian Journal of Medical Research 2008;127(3):256-262.

Koh JM, Park BL, Kim DJ, Kim GS, Cheong HS, Kim TH, et al. Identification of novel RANK polymorphisms and their putative association with low BMD among postmenopausal women. Osteoporos Int 2007;18:323-331. doi: 10.1007/s00198-006-0244-5

Kruk M, Ralston SH, Albagha OME. LRP5 polymorphisms and response to risedronate treatment in osteoporotic men. Calcif Tissue Int 2009;84(3):171-179. doi: 10.1007/s00223-008-9207-5

Lewiecki EM. Role of sclerostin in bone and cartilage and its potential as a therapeutic target in bone diseases. Therapeutic Advances in Musculoskeletal Disease 2014;6(2):48-57. doi: 10.1177/1759720X13510479

Lima CAD, Javorski NR, Souza APO, Barbosa AD, Valença APMC, Crovella S, et al. Polymorphisms in key bone modulator cytokines genes influence bisphosphonates therapy in postmenopausal women. Inflammopharmacology 2017;25(2):191-201. doi: 10.1007/s10787-017-0322-7

Liu Y, Liu HJ, Li M, Zhou PR, Xing XP, Xia WB, et al. Association of farnesyl diphosphate synthase polymorphisms and response to alendronate treatment in Chinese postmenopausal women with osteoporosis. Chin Med J (Engl) 2014;127(3):662-668. doi: 10.3760/cma.j.issn.0366-6999.20132382

Liu YJ, Shen H, Xiao P, Xiong DH, Li LH, Recker RR, et al. Molecular genetic studies of gene identification for osteoporosis: A 2004 update. Journal of Bone and Mineral Research 2006;21(10):1511-1535. doi: 10.1359/jbmr.051002

López-Delgado L, Riancho-Zarrabeitia L, Riancho JA. Genetic and acquired factors influencing the effectiveness and toxicity of drug therapy in osteoporosis. Expert Opin Drug Metab Toxicol 2016;12(4):389-398. doi: 10.1517/17425255.2016.1154533

Marini F, Brandi ML. Pharmacogenetics of osteoporosis. Best Practice and Research: Clinical Endocrinology and Metabolism 2014;28(6):783-793. doi: 10.1016/j.beem.2014.07.004

Marini F, Brandi ML. Pharmacogenetics of osteoporosis: What is the evidence? Curr Osteoporos Rep 2012;10(3):221-337. doi: 10.1007/s11914-012-0110-7

Marini F, Brandi ML. The future of pharmacogenetics for osteoporosis. Pharmacogenomics 2013;14(6):641-653. doi: 10.2217/pgs.13.40

Marini F, Falchetti A, Silvestri S, Bagger Y, Luzi E, Tanini A, et al. Modulatory effect of farnesyl pyrophosphate synthase (FDPS) rs2297480 polymorphism on the response to long-term amino-bisphosphonate treatment in postmenopausal osteoporosis . Curr Med Res Opin 2008;24(9):2609-15. doi: 10.1185/03007990802352894

Marini F, Brandi ML. Pharmacogenetics of Osteoporosis: Future Perspectives. Calcified Tissue International 2009;84(5):337-347. doi: 10.1007/s00223-009-9226-x

Mohammadi Z, Fayyazbakhsh F, Ebrahimi M, Amoli MM, Khashayar P, Dini M, et al. Association between vitamin D receptor gene polymorphisms (Fok1 and Bsm1) and osteoporosis: A systematic review. Journal of Diabetes and Metabolic Disorders 2014;13(1):98. doi: 10.1186/s40200-014-0098-x

Moran JM, Pedrera-Canal M, Rodriguez-Velasco FJ, Vera V, Lavado-Garcia JM, Fernandez P, et al. Lack of association of vitamin D receptor BsmI gene polymorphism with bone mineral density in Spanish postmenopausal women. PeerJ 2015;3:e953. doi: 10.7717/peerj.953

Nguyen T V., Eisman JA. Pharmacogenomics of osteoporosis: Opportunities and challenges. Journal of Musculoskeletal Neuronal Interactions 2006;6(1):62.

Ogawa S, Ouchi Y. [Therapeutic purpose and treatment guideline of osteoporosis]. Clin Calcium 2012;22(6):885. doi: CliCa1206885889

Olmos JM, Zarrabeitia MT, Hernández JL, Sãudo C, González-Macías J, Riancho JA. Common allelic variants of the farnesyl diphosphate synthase gene influence the response of osteoporotic women to bisphosphonates. Pharmacogenomics J 2012;12(3):227-232. doi: 10.1038/tpj.2010.88

Palomba S, Numis FG, Mossetti G, Rendina D, Vuotto P, Russo T, et al. Effectiveness of alendronate treatment in postmenopausal women with osteoporosis: Relationship with Bsml vitamin D receptor genotypes. Clin Endocrinol (Oxf) 2003;58(3):365-371. doi: 10.1046/j.1365-2265.2003.01724.x

Quandt SA, Thompson DE, Schneider DL, Nevitt MC, Black DM. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of -1.6 to -2.5 at the femoral neck: The fracture intervention trial. Mayo Clin Proc 2005;80(3):343-349. doi: 10.4065/80.3.343

Wagner ER, Zhu G, Zhang B-Q, Luo Q, Shi Q, Huang E, et al. The Therapeutic Potential of the Wnt Signaling Pathway in Bone Disorders. Curr Mol Pharmacol 2011;4(1):14-25. doi: 10.2174/1874467211104010014

Ralston SH. Osteoporosis as an hereditary disease. Clin Rev Bone Miner Metab 2010;8(2):68-76. doi: 10.1007/s12018-010-9073-3

Rapuri PB, Gallagher JC, Knezetic JA, Haynatzka V. Estrogen receptor alpha gene polymorphisms are associated with changes in bone remodeling markers and treatment response to estrogen. Maturitas 2006;53(4):371-379. doi: 10.1016/j.maturitas.2005.07.007

Riancho JA, Hernández JL. Pharmacogenomics of osteoporosis: A pathway approach. Pharmacogenomics 2012;13(7):815-829. doi: 10.2217/pgs.12.50

Russell RGG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: Similarities and differences and their potential influence on clinical efficacy. Osteoporosis International 2008;19(6):733-759. doi: 10.1007/s00198-007-0540-8

Sebba AI. Significance of a decline in bone mineral density while receiving oral bisphosphonate treatment. Clin Ther 2008;30(3):443-452. doi: 10.1016/j.clinthera.2008.03.008

Talaat RM, Sidek A, Mosalem A, Kholief A. Effect of bisphosphonates treatment on cytokine imbalance between TH17 and Treg in osteoporosis. Inflammopharmacology 2015;23(2-3):119-125. doi: 10.1007/s10787-015-0233-4

Tsoumpra MK, Muniz JR, Barnett BL, Kwaasi AA, Pilka ES, Kavanagh KL, et al. The inhibition of human farnesyl pyrophosphate synthase by nitrogen-containing bisphosphonates. Elucidating the role of active site threonine 201 and tyrosine 204 residues using enzyme mutants. Bone 2015;81:478-486. doi: 10.1016/j.bone.2015.08.020

Uitterlinden AG, Ralston SH, Brandi ML, Carey AH, Grinberg D, Langdahl BL, et al. The association between common vitamin D receptor gene variations and osteoporosis: A participant-level meta-analysis. Ann Intern Med 2006;145(4):255-264. doi: 10.7326/0003-4819-145-4-200608150-00005

Venegas KR, Gmez MA, Eisman JA, Sánchez AG, Dader MJF, Hernández MAC. Pharmacogenetics of osteoporosis-related bone fractures: Moving towards the harmonization and validation of polymorphism diagnostic tools. Pharmacogenomics 2010;11(9):1287-1303. doi: 10.2217/pgs.10.116

Wang C, Zheng H, He JW, Zhang H, Yue H, Hu WW, et al. Genetic polymorphisms in the mevalonate pathway affect the therapeutic response to alendronate treatment in postmenopausal Chinese women with low bone mineral density. Pharmacogenomics J 2015;15(2):158-164. doi: 10.1038/tpj.2014.52

Wang C, He J, Qin Y, Zhang H, Hu W, Liu Y, et al. Osteoprotegerin gene polymorphism and therapeutic response to alendronate in postmenopausal women with osteoporosis. Zhonghua Yi Xue Za Zhi 2009;89(42):2958-2962.

Wang JY, Zhou PR, Liu Y, Xu XJ, Ma DD, Xia WB, et al. The analysis of DKK1 polymorphisms in relation to skeletal phenotypes and bone response to alendronate treatment in Chinese postmenopausal women. Pharmacogenomics 2016;17(3):209-217. doi: 10.2217/pgs.15.167

Yao GQ, Wu JJ, Troiano N, Insogna K. Targeted overexpression of Dkk1 in osteoblasts reduces bone mass but does not impair the anabolic response to intermittent PTH treatment in mice. J Bone Miner Metab 2011;29(2):141-148. doi: 10.1007/s00774-010-0202-3

Yuan FL, Li X, Lu WG, Zhao YQ, Li CW, Li JP, et al. Type 17 T-helper cells might be a promising therapeutic target for osteoporosis. Mol Biol Rep 2012;39(1):771-774. doi: 10.1007/s11033-011-0797-z

Zheng H, Wang C, He JW, Fu WZ, Zhang ZL. OPG, RANKL, and RANK gene polymorphisms and the bone mineral density response to alendronate therapy in postmenopausal Chinese women with osteoporosis or osteopenia. Pharmacogenet Genomics 2016;26(1):12-19. doi: 10.1097/FPC.0000000000000181

Zhou PR, Liu HJ, Liao EY, Zhang ZL, Chen DC, Liu J, et al. LRP5 polymorphisms and response to alendronate treatment in Chinese postmenopausal women with osteoporosis. Pharmacogenomics 2014;15(6):821-831. doi: 10.2217/pgs.14.12

Zhou PR, Xu XJ, Zhang ZL, Liao EY, Chen DC, Liu J, et al. SOST polymorphisms and response to alendronate treatment in postmenopausal Chinese women with osteoporosis. Pharmacogenomics 2015;16(10):1077-1088. doi: 10.2217/pgs.15.76

Authors

•Alina Deniza Ciubean, Department of Rehabilitation Medicine "Iuliu Haţieganu" University of Medicine and Pharmacy, 46-50, Viilor Street, Cluj-Napoca, PC 400437, Romania, EU, email: alina.deniza.ciubean@gmail.com

• Laszlo Irsay, Department of Rehabilitation Medicine "Iuliu Haţieganu" University of Medicine and Pharmacy, 46-50, Viilor Street, Cluj-Napoca, PC 400437, Romania, EU, email: laszloirsay@gmail.com

•Rodica Ana Ungur, Department of Rehabilitation Medicine "Iuliu Haţieganu" University of Medicine and Pharmacy, 46-50, Viilor Street, Cluj-Napoca, PC 400437, Romania, EU, email: rodica.ana.ungur@gmail.com

•Viorela Mihaela Ciortea, Department of Rehabilitation Medicine "Iuliu Haţieganu" University of Medicine and Pharmacy, 46-50, Viilor Street, Cluj-Napoca, PC 400437, Romania, EU, email: viorela.ciortea@yahoo.com

•Ileana Monica Borda, Department of Rehabilitation Medicine "Iuliu Haţieganu" University of Medicine and Pharmacy, 46-50, Viilor Street, Cluj-Napoca, PC 400437, Romania, EU, email: monicampop@yahoo.fr

•Dogaru Gabriela Bombonica, Department of Rehabilitation Medicine "Iuliu Haţieganu" University of Medicine and Pharmacy, 46-50, Viilor Street, Cluj-Napoca, PC 400437, Romania, EU, email: dogarugabrielaumf@gmail.com

•Ioan Onac, Department of Rehabilitation Medicine "Iuliu Haţieganu" University of Medicine and Pharmacy, 46-50, Viilor Street, Cluj-Napoca, PC 400437, Romania, EU, email: onac.ioan@yahoo.com

•Adrian Pavel Trifa, Department of Medical Genetics "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania, EU, email: trifa.adrian@gmail.com

•Cristian Marius Voina, "Department of Medical Genetics "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania, EU, email: voinacristianm@gmail.com

•Stefan Cristian Vesa, Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Haţieganu University of Medicine and Pharmacy, 23 Gheorghe Marinescu Street, Cluj-Napoca, Romania, email: stefanvesa@gmail.com

•Anca Dana Buzoianu, Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Haţieganu University of Medicine and Pharmacy, 23 Gheorghe Marinescu Street, Cluj-Napoca, Romania, email:ancabuzoianu@yahoo.com

Citation	Ciubean AD, Irsay L, Ungur RA, Ciortea VM, Borda IM, Dogaru GB, Onac I, Trifa AP, Voina CM, Vesa SC, Buzoianu AD. Genetic factors influencing the efficiency of alendronate therapy in postmenopausal women with primary osteoporosis. HVM Bioflux 2019;11(2):66-74.
Editor	Antonia Macarie
Received	28 January 2019
Accepted	3 May 2019
Published Online	19 May 2019
Funding	None reported
Conflicts/ Competing Interests	None reported