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Helicobacter Pylori Positive Peptic Ulcer Disease: Antibiotic Resistance to First Line Therapy

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Helicobacter pylori is a gram-negative bacterium that was first identified in 1982. Since that time, several studies and surveys have demonstrated the importance of *H. pylori* as one of the major etiological factors in chronic gastritis, peptic ulcer disease (PUD), and stomach cancer (**Table 1**).[1,2] *H. pylori* is considered the most common chronic infection worldwide and in the United States it is estimated the percentage of the population infected by this bacteria is 30-40%.[2] In the United States alone, it is estimated that PUD affects > 6 million people every year and data from the Nationwide Inpatient Sample database shows that there were a total of 1,453,892 hospitalizations for PUD from 1998-2005.[3,4] Sandler et al., estimated the US economic burden of PUD was greater than 3.1 billion dollars in 1998 costs. This burden was the 4th highest for gastrointestinal diseases in their study, behind only gastroesophageal reflux disease (GERD), gallbladder disease, and colorectal cancer.[5]

Studies performed after the discovery of *H. pylori* as a causative agent of PUD have shown that the eradication of the infection leads to ulcer healing, a decrease in recurrence, and greater symptom relief.[5] Before the advent of antibiotics in the eradication of *H. pylori*, treatment options were limited to lifestyle changes, long-term acid suppression and vagotomy. Sonnenberg et al., evaluated the costs of each of these treatment options and showed that antibiotic treatment was the most cost effective option for treating PUD (**Table 2**).[7]

Presently, the consensus treatment for *H. pylori* positive PUD is triple therapy with two antibiotics and a proton pump inhibitor.[1,8] However, antibiotic usage inevitably promotes the selection and spread of resistant strains of *H. pylori*. Recent studies have shown that the first line antibiotics clarithromycin, metronidazole, and amoxicillin have experienced a drop in efficacy due to the emergence of resistant strains of bacteria.[9-11] The purpose of this article is to review possible mechanisms of resistance to the first line antibiotics, incidence rates of resistant *H. pylori* strains, and recommendations for treatment of resistant infections.

Treatment Regimens: Guideline Recommendations

Both the European Helicobacter Pylori Study Group (EHPS) and American College of Gastroenterology (ACG) have released updated guidelines on the treatment of *H. pylori*.[1,8] The EHPS and the ACG first line therapy recommendations include clarithromycin (500mg twice daily), a PPI (standard dosing), and amoxicillin (1 gram twice daily), or the same combination with substitution of amoxicillin by metronidazole (400 or 500 mg twice daily).[1,8] The EHPS suggests that these regimens should only be used if known population resistance of clarithromycin is less than 15-20%.[8]

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Table 1 | Incidence of *H. pylori* in gastric diseases.[6]

Disease State	Incidence, %
Duodenal Ulcer	50-75
Gastric Ulcer	65-95
Dyspepsia	20-60
Gastric Cancer	70-90

Table 2 | Cost evaluation of PUD treatments.[7]

Treatment	Cost in 1993 USD
Antibiotic Therapy	$995
Long-term acid suppression	$11,186[a]
Ulcer surgery (selective vagotomy)	$17,661[a]

[a] Figures have been extrapolated out to 15 years of therapy due to the lack of eradication with the treatment.

The ACG states that clinicians should be aware that resistance could be a problem and cites Vakil et al., whose multicenter study of 3, 7, and 10 day triple therapy showed that none of the first-line antibiotic regimens achieved greater than 78% eradication rates.[12] **Table 3** contains common treatment regimens and associated patient cost.

Mechanism of Resistance

Clarithromycin

Resistance to clarithromycin is an important consideration due to its inclusion as a major component of the first line treatment regimens.[14] The mechanism of action for clarithromycin resistance in *H. pylori* is associated with three point mutations in the 23s rRNA gene.[15] These point mutations are A2143G, A2142G, and A2142C. Each of these mutations can cause conformational changes in the peptidyl transferase loop of domain V of the 23s ribosomal RNA, causing a decrease in the binding affinity of clarithromycin to bacterial ribosomes.[16] This resistance is selected through increased antibiotic use and is subsequently passed along via vertical transmission to bacterial progeny.

Metronidazole

Metronidazole resistance is a much larger concern in developing countries due to its availability over the counter, inexpensiveness, and its usage to treat parasitic infections indigenous to the local areas. Some studies have shown that resistance to metronidazole can be above 90% in these countries.[14] The basis of resistance for metronidazole is the lack of its activation inside the *H. pylori* bacteria into its active reduced form.[17] There is some evidence that shows metronidazole resistance may be combated by longer durations and the usage of higher doses.[1,8]

Amoxicillin

Presently, resistance to amoxicillin is negligible with no appreciable effect on clinical eradication rates.[1, 8] However, newer studies show that amoxicillin resistant strains are on the rise and could soon be a major factor in treatment decisions of *H. pylori* infections.[18] DeLoney et al., evaluated a selected strain of amoxicillin resistant *H. pylori* where two distinct mechanisms of resistance were identified. This particular strain overcame amoxicillin's effects through altered penicillin binding proteins and either a diffu-

Table 3 | Common treatment regimens for *Helicobacter pylori* eradication.[13]

Regimen	Duration	Estimated total regimen cost to patient[a]
omeprazole (Prilosec®) 20 mg twice daily, amoxicillin (Amoxil®) 1 g twice daily, clarithromycin (Biaxin®) 500 mg twice daily	14 days	$150.64
lansoprazole (Prevacid®) 30 mg twice daily, amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily	10 to 14 days	$141.80-170.52
omeprazole 20 mg twice daily, metronidazole (Flagyl®) 500 mg twice daily, clarithromycin 500 mg twice daily	14 days	$132.96
Bismuth subsalicylate (Pepto-Bismol®) 525 mg four times daily, metronidazole 250 mg four times daily, tetracycline (Sumycin®) 500 mg four times daily, histamine H_2 blocker	14 days (additional 14 days of H_2 blocker treatment only)	$41.72

[a] Costs obtained from www.drugstore.com on 9/18/2010; generics used when available.
[b] Ranitidine was used as the H_2 blocker of choice.

Table 4 | Comparison of primary resistance prevalence in different parts of the world.[20]

Country	Years	Type of Study	# strains tested	Clarithromycin Resistance (%)	Metronidazole Resistance (%)	Amoxicillin Resistance (%)	Reference
Germany	95-00	MonoC	1644	2.2	26.2	0	Wolle[21]
Italy	98-02	MonoC	406	23.4	36.7	0.2	Torachio[22]
Spain	95-98	MonoC	235	12.9	23.5	0	Cuchi Burgos[23]
United Kingdom	95-98	MonoC	843	3.9	36	0.4	Teare[24]
Mexico	95-97	MonoC	144	25	76.3	0	Torres[25]
USA[a]	93-99	MultiC	3439	11.1	21.6	0.08	Osato[26]
USA[a]	93-99	MultiC	3624	10.1	36.9	1.4	Meyer[27]
Iran	02	BiC	203	9.8	53	ND	Mohammadi[28]
Hong Kong	97-01	MonoC	991	4.5	2.9	0.3	Ling[29]
Japan	95-00	MonoC	593	11	9	0.3	Perez Aldana[30]
Korea	94-99	BiC	456	5.9	40.6	0	Kim[31]
Singapore	93-96	MonoC	459	ND	62.7	ND	Teo[32]
New Zealand	93-98	MonoC	225	6.8	32	ND	Fraser[33]

ND = Not Determined; **MonoC** = single center; **MultiC** = multiple centers; **BiC** = two centers.
[a] Denotes studies discussed in text.

sion barrier or efflux pump mechanism limiting the amount of amoxicillin allowed into the cell.[19]

STUDIES ON *H. PYLORI* RESISTANCE

Please refer to **Table 4**, for a summary of antibiotic-resistant *H. pylori* prevalence for the US and worldwide.

Pattern of Primary Resistance of Clarithromycin or Metronidazole

Osato et al, evaluated the frequency of primary claritrhromycin and metronidazole resistance among *H. pylori* isolated from patients enrolled in 17 US-based antibiotic treatment trials between 1993 and 1999.[2] Data was categorized by patient age, sex, and region of the United States.[19] The database consisted of 3439 samples of which prevalence rates of clarithromycin and metronidazole resistance were calculated. Over the 7 years, rates of resistance to clarithromycin varied (P=0.05) with a combined overall resistance of 11.1% and a range from 6.1% to 14.5%. Metronidazole resistance differed based upon which test method was used, E-test or agar dilution. For the E-test, metronidazole resistance was 39% versus 25.2% when determined with the agar dilution method (P<0.001). Women were more likely than men to have a metronidazole-resistant strain of *H. pylori* (63% vs 35.1%, respectively, as determined by E-test [P=0.01] and 34.7% vs 22.6%, respectively, as determined by agar dilution [P=0.03]). Women were also more likely to have clarithromycin resistant strains of *H. pylori* as well, but the difference (14.1% to 9.7%) was not statistically significant (P=0.06). Age played a factor in resistance determination with those over 70 years of age having lower incidence of *H. pylori* resistance strains than those people aged between 20 and 70. When compared, metronidazole *H. pylori* resistance strains decreased from 50% in the middle-aged population (20 to 70 yo) to 31% in people over 70 years (P=0.05). Those over 70 were also less likely to have a clarithromycin resistant strain as well (P<0.05). There was no statistical variation in *H. pylori* resistance incidence for differing geographic locations (P>0.20).

The Surveillance of H. pylori Antimicrobial Resistance Partnership (SHARP) Study, 1993–1999

In a meta-analysis by Meyer et al, patient-level data was used to estimate the prevalence of *H. pylori* resistance to antimicrobials in the United States, to characterize risk factors associated with resistance, and to explore association between drug utilization and antimicrobial resistance over time.[27] Data was gathered from 20 nationwide *H. pylori* eradication trials in the United States between the years of 1993 to 1999. Meta-analysis of this information was used to combine information about the relationship between *H. pylori* resistance and eight risk factors, including geographic location, age, sex, year of enrollment, ethnicity, ulcer status, test method, and study. In the meta-analysis, overall clarithromycin-resistance prevalence

was 10.1% (95% CI, 9.1% to 11.1%) and multivariable analyses showed that resistance was significantly associated with geographic region (P = 0.050), older age (P < 0.001), female sex (P < 0.001), inactive ulcer disease (P < 0.001), and study (P = 0.010). Clarithromycin resistant *H. pylori* was more likely in the mid-Atlantic and northeastern regions of the US, older patients, women, and patients with an inactive ulcer. Overall, metronidazole resistance was 36.9% (CI, 35.1% to 38.7%) with significant association with female sex (P < 0.001), Asian ethnicity (P < 0.001), year of study enrollment (p = 0.036), test method used (P = 0.002), and study (P < 0.001). Metronidazole resistance was higher in females, Asians, those enrolled earlier, and in those where E-test was used. The incidence of amoxicillin resistant *H. pylori* was low overall and none of the covariates were significantly associated with increased amoxicillin resistance. The authors also investigated the occurrence of *H. pylori* dual resistance to both clarithromycin and metronidazole. Approximately 3.9% (CI, 3.2% to 4.7%) of the tested isolates were positive for dual resistance. Dual resistance was significantly associated with sex (P < 0.001), age (P = 0.001), and ethnicity (P = 0.03). Higher incidence of dual resistant *H. pylori* strains were found in women, those aged greater than 40 years, and those of Asian ethnicity. The authors observed that pretreatment antimicrobial resistance is associated with a negative impact on treatment efficacy with clarithromycin being the most compromised. The clarithromycin resistance affects dual therapy (95.1% failure rate) more so than triple therapy (68.6% failure rate), but does lead to the need for salvage therapy in affected individuals. Metronidazole resistance is associated with a reduction in efficacy of approximately 37.7% in triple therapy regimens but quadruple-therapy regimens (PPI, bismuth, tetracycline, and metronidazole) were equally effective in treating both metronidazole-susceptible and metronidazoale-resistant strains (92%, range 63%-100%), if given for longer than 7 days.

Treatment for Resistant *H. pylori* Infections

With the decreasing eradication rates of clarithromycin based therapy in the United States, there is an emerging need for therapies to treat patients with primary resistance and those who fail their initial therapy regimens.[14] The ACG recommends that initial clarithromycin based triple therapy should be given for 14 days to achieve greater than 80% eradication rate, which 3-, 7-, and 10-day durations do not achieve.[1] In persistent *H. pylori* infection, effort should be made to avoid the use of any antibiotics that the patient may have previously taken, including macrolides, quinolones, and nitroimidazoles due to the high likelihood of pressure selection of resistant strains by exposure.[22]

FDA-approved second line therapy includes a 10-14 day quadruple regimen of bismuth, a PPI, tetracycline, and metronidazole. This regimen is also approved as an alternate 1st line therapy. The disadvantage with this regimen is the daily pill burden, up to 18 pills a day, and the four times daily dosing frequency.[1] Several studies have tested alternative salvage therapies that have not received US approval. Perri et al, used a 10 day course of rifabutin 150mg/300mg once daily, pantoprazole 40 mg twice daily, and amoxicillin 1g twice daily to achieve an eradication rate of 87% in resistant *H. pylori* infections.[34] Bilardi, et. al. studied a 10 day regimen of panatoprazole 40mg, amoxicillin 1g, and levofloxacin 250mg, all given twice daily which yielded a 70% eradication rate in resistant *H. pylori* infections.[35] Finally, sequential therapy lasting 10 days, involving a PPI (standard dose twice daily) and amoxicillin (1g twice daily) for 5 days followed by 5 days of a PPI (standard dose twice daily), clarithromycin (500mg twice daily), and tinidazole (500mg twice daily) achieved an 89% eradication rate in patients with documented clarithromycin resistance.[36]

Summary

Almost three decades have passed since Helicobacter pylori was discovered and implicated as a major causative factor in peptic ulcer disease. Through increased antibiotic use and vertical transmission of resistance mutations, *H. pylori* has gradually blunted the efficacy of first line triple therapy to a point where persistent infections have become almost a 1 in 5 occurrence. Several 2nd line antibiotic therapy regimens are available for those patients failing 1st line therapy. Even with emerging resistance, antibiotic therapies are the most effective overall treatment for *H. pylori* positive PUD.

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DENOSUMAB (PROLIA®): TWICE-YEARLY TREATMENT FOR OSTEOPOROSIS

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Osteoporosis is a skeletal disease characterized by low bone mass and structural deterioration of bone tissue.[1] Diagnosis is most commonly made via dual energy X-ray absorptiometry (DXA) scan. A DXA scan determines a patient's bone mineral density (BMD). The patient's number of standard deviations above or below the mean BMD of a normal young adult with the same gender is recorded as a T-Score (**Table 1**). A T-score below -2.5 is defined by the World Health Organization (WHO) as osteoporosis.[2]

Based on data from the National Health and Nutrition Examination Survey III (NHANES III), the National Osteoporosis Foundation (NOF) estimates that ≥ 10 million Americans have osteoporosis and an additional 33.6 million have low bone density of the hip.[3] To put this into more relative terms, approximately 50% Caucasian women and 20% men will experience an osteoporosis-related fracture at some point in their lifetime.[1] Hip fractures result in 10 to 20 percent excess mortality within one year and are associated with 2.5 fold increase in future fractures.[1,4] Twenty percent of hip fracture patients require long-term nursing home care and only 40 percent fully regain their pre-fracture level of independence.[1]

In 2004, osteoporosis-related fractures in the US were responsible for roughly 432,000 hospital admissions, 2.5 million medical office visits and 180,000 nursing home admissions.[1] The cost to the healthcare system associated with osteoporosis-related fractures was estimated in 2005 at $17 billion; hip fractures accounted for 14% of incident fractures and 72% of fracture costs.[5] Due to the aging population, the Surgeon General estimates that the number of hip fractures and their associated costs could double or triple by the year 2040.

The 2010 NOF Clinician's Guide for the prevention and treatment of osteoporosis recommends initiation of treatment for patients that have at least 1 of 3 prerequisites (**Table 2**).

C. Everett Koop said, "Drugs don't work in patients who don't take them...." Poor adherence to osteoporosis medications is associated with a significantly greater risk of fractures. The current trend of less frequent regimens aims to increase patient convenience and adherence.[7]

Current FDA-approved pharmacologic options for treating osteoporosis are bisphosphonates (alendronate [Merck], risendronate [Warner Chilcott], ibandronate [Roche], and zoledronic acid [Novartis]), calcitonin (calcitonin-salmon [Novartis]), selective estrogen receptor modulators (raloxifene [Lilly]), and recombinant parathyroid hormone (teriparatide [Lilly]). Denosumab (Prolia®; Amgen) was approved by the FDA on June 1, 2010 for postmenopausal osteoporosis (PMO). The main purpose of this article will be to discuss dosing, safety, efficacy, and cost of denosumab.

CLINICAL PHARMACOLOGY

Normally, adult bone is restructured through a balanced process of degradation by osteoclasts and rebuilding by osteoblasts. Osteoblasts produce receptor activation of nuclear factor-kappaB (RANKL) ligand and osteoprotegerin (OPG). RANKL binds to

Table 1 | WHO classification of T-scores.[2]

T-Score	Interpretation
> -1	Normal bone density
-1 to -2.5	Osteopenia; may lead to osteoporosis
< -2.5	Osteoporosis

Table 2 | Criteria for treatment of osteoporosis.[6]

Hip or vertebral (clinical or morphometric) fractures.
BMD T-scores ≤ -2.5 at the femoral neck or spine by DXA
Postmenopausal women and men age 50 and older with osteopenia at the femoral neck or spine and a 10-year hip fracture probability ≥ 3% or a 10-year major osteoporosis-related fracture probability ≥ 20% based on the US-adapted WHO absolute fracture risk model (FRAX®; www.NOF.org and www.shef.ac.uk/FRAX).

Table 3 | Pharmacokinetics of denosumab.[9]

C_{max}	6.75 ± 1.89 mcg/mL
T_{max}	10 days (3 to 21 days)
$t_{1/2}$ (n = 46)	25.4 ± 8.5 days
$AUC_{0\text{-}16\ weeks}$	316 ± 101 mcg/day/mL

RANK on osteoclast precursor cells to activate osteoclasts. OPG is a potent inhibitor of osteoclast formation and a decoy receptor for RANK. The relative ratio of OPG and RANK ligand in the bone marrow microenvironment may determine the number of active osteoclasts, bone resorption rate, and bone mass.[8] Denosumab is a monoclonal antibody that mimics endogenous osteoprotegerin thereby inhibiting osteoclast formation, function, and survival, decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.[9]

Pharmacokinetics

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (CHO) by recombinant DNA technology. The pharmacokinetics of denosumab were determined in a study conducted in healthy male and female volunteers (n = 73, age range: 18 to 64 years) following a single subcutaneous 60 mg dose after fasting (**Table 3**).[9]

No accumulation or change in denosumab pharmacokinetics with time was observed upon multiple dosing of 60 mg subcutaneously administered once every 6 months. Furthermore, showed no notable differences in pharmacokinetics have been observed according to age (in postmenopausal women), race, or body weight (36 to 140 kg). No drug-drug interaction studies have been published to date with denosumab. In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab; thus, dose adjustment for renal impairment is not recommended. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab.[9]

Clinical Trials

Table 4 compares the risk reduction in vertebral, hip, and non-vertebral fracture risk reduction for currently marketed FDA approved PMO treatments.

A multicenter, placebo-controlled, dose-response study enrolled Japanese ambulatory PMO women ≤ 80 years old (mean 65.1 ± 6.8 years) with T-scores between -2.5 and -4.0 at the lumbar spine or between -2.5 and -3.5 at the femoral neck or total hip (**Table 5**).[20] Subjects were randomly assigned to 4 parallel treatment cohorts using AMG 162 (denosumab) 14, 60 and 100mg or placebo. Each product was administered by subcutaneous injection at day 1 and month 6. Eighty five percent of subjects (n=143) assigned to denosumab and 91% (n=52) assigned to placebo completed the study. Denosumab doses of 14mg Q6M did not maintain sufficient suppression of bone turnover markers over the entire dosing interval. The additional efficacy observed by increasing the dose from 60 mg to 100 mg Q6M was inconsistent. Thus, denosumab 60 mg Q6M was selected for future clinical studies. Serious adverse events were reported for 11%, 7%, and 4% of subjects in the 14, 60, and 100mg denosumab dose groups, respectively and 7% of subjects in the placebo group. Similar to efficacy endpoints, no clear dose-response relationship was observed for adverse effects.

Miller PD et al. conducted a 48 month dose-ranging study at 29 study centers in the US.[21] In this study, women ≤ 80 years old had BMD T-scores of -1.8 to -4.0 at the lumbar spine or -1.8 to -3.5 at the femoral neck or total hip. For the first 24 months, patients were randomly allocated to one of 8 blinded or 1 open-label treatment cohort. For the primary outcome, lumbar spine BMD percent change from baseline at month 12, mean changes were -0.81±0.48, 4.41±0.5, 4.71±0.5, 6.69±0.54, 3.03±0.43, 4.55±0.47, 5.52±0.49, and 5.07±0.47% for placebo, 6, 14, and 30mg Q3M, 14, 60, 100, and 210mg Q6M groups, respectively. This study was extended for an additional 24 months with denosumab 60mg or placebo Q6M. Based on the first 24 months of data, denosumab 60mg Q6M was selected for phase III trials. The subsequent 24 months of the study used patients who were previously using other doses or schedules of denosumab (6 or 14 mg Q3M and 14, 60, and 100mg Q6M). Compared with placebo, denosumab significantly reduced biochemical markers of bone turnover (CTX and NTX). The effect of discontinuing denosumab on BMD was investigated in patients using the highest (210 mg) dosage of denosumab Q6M. Twenty-four months after discontinuing 120 mg denosumab Q6M, bone loss plateaued at values near baseline; CTX, NTX and bone ALP increased to values above baseline and greater than those in the placebo group. To determine the effect of retreatment, subjects received 30mg denosumab Q3M for 24 months, placebo the next 12 months, then 60 mg denosumab Q6M. At 48 months, BMD increased 1.8% from baseline and BTM levels were similar to the continuous treatment group. Treatment related adverse events were not statistically significant between deno-

Table 4 | Comparison of vertebral, hip, and non-vertebral risk reduction with FDA-approved PMO treatments.

Drug (Brand Name)	Vertebral				Hip				Non-vertebral			
	Study	RRR	ARR	NNT	Study	RRR	ARR	NNT	Study	RRR	ARR	NNT
Alendronate (Fosamax®)	FIT[10] (3yr)	47%	7%	14	FIT[10] (3yr)	51%	1.1%	90	FOSIT[11] (1yr)	47%	0.9%	111
Ibandronate (Boniva®)	BONE[12] (3yr)	49%	2.5%	40	n/a	n/a	n/a	n/a	BONE[12] (3yr)	69% (T score <-3)	N/A	N/A
Risendronate (Actonel®)	VERT[13] (USA-3yr)	41%	5%	20	HIP[14] (3yr)	40%	13%	77	VERT[13] (USA-3yr)	40%	3.2%	31
Zoledronic Acid (Reclast®)	HORIZON[15] (3yr)	70%	7.6%	13	HORIZON[15] (3yr)	41%	1.1%	91	HORIZON[15] (3yr)	25%	2.7%	37
Denosumab (Prolia®)	Cummings SR, et al.[16] (3yr)	68%	4.8%	21	Cummings SR, et al.[16] (3yr)	40%	0.3%	333	Cummings SR, et al.[16] (3yr)	20%	1.5%	67
Teriparatide (Forteo®)	Neer RM, et al.[17] (21mos)	65%	9%	11	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Raloxifene (Evista®)	RUTH[18] (5yr)	35%	0.6%	167	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Calcitonin-Salmon (Miacalcin®)	PROOF[19] (3yr)	34%	10%	10	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

ARR = Absolute Risk Reduction; **NNT** = Number Needed to Treat; **RRR** = Relative Risk Reduction; **n/a** = data not available.

sumab and placebo (p=0.8457).

The Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months) enrolled 7868 PMO women.[16] The mean BMD T-Scores were -2.8 at the lumbar spine, -1.9 at the total hip, and -2.2 at the femoral neck. Approximately 24% of women had vertebral fracture at baseline. Of 7868 subjects recruited, 6478 (82%) completed 36 months of study and 5979 (76%) received all injections. Subjects were randomly assigned to receive either placebo (n=3906) or 60mg denosumab (n=3902) subcutaneously every 6 months for 36 months. The reduction in risk for new radiographic vertebral fracture was similar during each year of the trial, with 61% RRR in 0-12 months (p<0.01), 78% RRR in >12-24 months (p<0.01), and 65% RRR in >24-36 months (p<0.01).

Comparison Trials

In a study by Seeman et al., 247 PMO women were recruited for a international, active-controlled parallel -group study.[22] Subjects were randomly assigned 1:1:1 to subcutaneous injection of denosumab 60mg Q6M with placebo tablets once weekly (n=83), oral alendronate 70mg weekly with placebo subcutaneous injections Q6M (n=82), or placebo tablets and injections (n=82). After 12 months, total, cortical, and trabecular BMD and cortical thickness at the distal radius decreased in the placebo group. The mean differences in cortical thickness for the distal radius in placebo, alendronate, and denosumab groups were -0.8%, 2.4%, and 3.4%, respectively. Denosumab failed to significantly increase trabecular BMD or cortical thickness compared with alendronate. Similar to the primary outcome result, denosumab failed to significantly increase distal tibia trabecular BMD and cortical thickness relative to alendronate. The incidence of adverse events did not differ by group--serious adverse events were reported in 5 subjects in the placebo group (6%), 5 subjects in the alendronate group (6.2%), and 2 subjects in the denosumab group (2.4%).

Kendler and colleagues studied the transition from alendronate to denosumab (STAND) in an international multicenter trial.[23] Subjects assigned to alendronate received subcutaneous placebo injections every 6 months, whereas, subjects assigned to denosumab received placebo tablets to take once weekly. This study did not utilize a placebo only group. The subjects had a mean age of 67.6 years, average of 19.3 years since menopause, were treated with a bisphosphonate for a median of 36 months (6 to 192 months)

Table 5 | Summary of denosumab clinical trials.

Study	Design	Dose	Results

Amgen (2008)[20]	• 1-y, phase II, R, DB, safety/efficacy study
	• Ambulatory PMO Japanese women ≤ 80 yrs old
	• Primary efficacy endpoint: Lumbar-spine BMD % change from baseline
	• Primary safety endpoint: incidence of treatment –emergent adverse events over 12 months
		• PCB (n = 52)
		• Denosumab 100 mg (n = 45)
		• Denosumab 60 mg (n = 50)
		• Denosumab 14 mg (n = 48)
		• All received ≥ 600 mg elemental Ca and ≥ 400 IU vitamin D
			• BMD increases significantly in all denosumab groups at month 12 compared with placebo:
			  • 7% (5.76-8.24) for 100 mg Q6M (p<0.001)
			  • 6.27% (5.06-7.49) for 60 mg Q6M (p<0.001)
			  • 5.25% (4.1-6.4) for 14 mg Q6M (p<0.001)
			• No difference in adverse events between treatments

Miller PD, et al.[21]	• 4-yr, phase II, R, DB, PC, dose ranging study
	• Postmenopausal women ≤80 yrs old with BMD T-score -1.8 to -4.0
	• Primary endpoint: lumbar spine BMD % Δ from baseline at month 12
	• Secondary endpoints: serum CTX % Δ from baseline at month 12, 24, 36, 42, and 48; urine NTX/Cr % Δ from baseline at month 12, 24, 36, 42, and 48; lumbar spine BMD % Δ from baseline at month 12 (alen), 24, 36, 42, and 48 (denos)
		• PCB (n=46)
		• Alendronate 70mg QW (n=47)
		• Denosumab
		  • 100mg Q6M (n=42)
		  • 6mg Q3M (n=44)
		  • 14mg Q3M (n=44)
		  • 30mg Q3M (n=41)
		  • 14mg Q6M (n=54)
		  • 60mg Q6M (n=47)
		  • 210mg Q6M (n=47)
			• Continuous, long-term denosumab treatment increased BMD at the lumbar spine (9.4 - 11.8%) and total hip (4.0 - 6.1%).
			• BTM consistently suppressed over 48 months, but increased with discontinuation and decreased with retreatment
			• Discontinuation of denosumab was associated with a BMD decrease of 6.6% at the lumbar spine and 5.3% at the total hip within the first 12 months of treatment discontinuation.
			• Retreatment with denosumab increased lumbar spine BMD by 9.0% from original baseline values
			• Adverse event rates were similar among treatment groups

Cummings SR et al.[16]	• 3-yr, phase III, R, DB, PC, treatment study • Women 60-90 yrs old with BMD T-Score at hip or spine -2.5 to -4.0 • Primary endpoint: reduction in the number of new vertebral fractures in PMO women compared with PCB • Secondary endpoint: time to first non-vertebral and/or hip fracture(s)	• PCB (n=3906) • Denosumab 60mg Q6M (n=3902) • All received 1000 mg Ca and vitamin D (≥ 800 IU if baseline 25-hydroxyvitamin D level between 12 -20 ng/ml, or ≥ 400 IU if baseline level > 20 ng/ml) daily	• Compared with PCB, denosumab reduced the relative risk of new radiographic fracture • Vertebral facture 68% RRR, 4.8% ARR, NNT 21, p < 0.001 • Non-vertebral fracture 20% RRR, 1.5% ARR, NNT 67, p<0.01 • Hip fracture 40% RRR, 0.3% ARR, NNT 333, p < 0.04 • No increase cancer, infection, CVD, delayed fracture healing, or hypocalcemia. • No cases of ONJ or adverse reactions to denosumab injection
Seeman E et al.[22]	• 1-yr, phase II, R, DB • Women between 50-70 yrs of age with PMO (T-scores between -2.0 and -3.0) • Primary endpoint: Cortical thickness of radius by XtremeCT % Δ from baseline at month 12 • Secondary endpoint: Cortical thickness of tibia by XtremeCT % Δ from baseline at month 12	• PCB (n= 79) • Denosumab 60mg Q6M (n= 78) • Alendronate 70mg QW (n=73) • All received ≥500 mg Ca + vitamin D (≥800 IU if baseline 25-hydroxyvitamin D level 12-20 ng/ml, or ≥400 IU if > 20 ng/ml) daily	• Distal radius cortical thickness: PCB -0.8%, alendronate 2.4%, denosumab 3.4% (failed to significantly increase cortical thickness compared to alendronate) • Distal tibia cortical thickness: PCB 1.4%, alendronate 4.9%, denosumab 5.8% (failed to significantly increase distal tibia cortical thickness relative to alendronate)
Kendler DL et al.[23]	• 1-yr, phase III, R, DB, safety/efficacy study • Ambulatory postmenopausal women ≥ 55 yrs with lumbar spine or total hip BMD T-score ≤ -2 and ≥ -4. • Primary endpoint: % Δ in total hip BMD from baseline to month 12. • Secondary endpoints: % Δ from baseline in serum CTX-1 at month 3 and the % Δ from baseline in lumbar spine BMD at month 12	• Alendronate 70mg QW (n=251) • Denosumab 60mg Q6M (n=253) • All received 1000 mg Ca and ≥400 IU vitamin D daily for the entire study and alendronate 70mg QW for 1 month before being randomly assigned to either continued weekly alendronate or subcutaneous denosumab.	• Alendronate: total hip BMD increased 1.05% by month 12 • Denosumab: total hip BMD increased 1.9% by month 12 (p<0.0001 for comparison of total hip BMD). • Greater BMD gains with denosumab compared with alendronate at month 12 at the lumbar spine, femoral neck, and 1/3 radius (all p<0.0125). • Median serum CTX levels significantly decreased at all time points with denosumab compared to alendronate (p<0.0001) • No difference in adverse events between the two groups

Δ = change; **ARR** = absolute risk reduction **BMD** = bone mineral density; **DB** = double-blind; **NNT** = numbers needed to treat; **PC** = placebo-controlled; **PCB** = placebo; **R** = randomized; **RRR** = relative risk reduction

immediately before screening, and had an average BMD T-score at the total hip and lumbar spine of -1.80 and -2.63, respectively. Fifty percent of these subjects had previous osteoporosis related fractures and 43% had received generic alendronate before screening. After 12 months, adverse events were reported in 78% of denosumab and 79% of alendronate subjects (p=0.8294), whereas, serious adverse events were reported in 5.9% of denosumab and 6.4% of alendronate -treated subjects (p=0.8546).

Active Studies

An Open Label, Single Arm, Extension Study to Evaluate the Long Term Safety and Sustained Efficacy of denosumab in the Treatment of Postmenopausal Osteoporosis started August 2007 and is estimated to be complete by August 2015.[24] Other ongoing studies are summarized in **Table 6.**

Safety Concerns

Hypocalcemia is currently the only absolute contraindication.[9] Since hypocalcemia may be exacerbated by the use of denosumab, pre-existing hypocalcemia must be corrected prior to initiating therapy with denosumab. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is recommended during treatment. In addition, patients should maintain calcium levels with adequate calcium and vitamin D supplementation.

Adverse Effects

Table 7 summarizes the adverse events experienced with denosumab compared with placebo during the FREEDOM Trial.[16] No significant differences were observed between denosumab and placebo groups for the total incidence of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events.

Serious Infections

In the FREEDOM trial, there was no difference in serious infections (skin, abdomen, urinary tract, ear, and endocarditis) between those treated with denosumab compared with placebo.[16] Additionally, the incidence of opportunistic infections was balanced between placebo and denosumab group. Patients that develop signs or symptoms of severe infection should seek prompt medical attention. Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections.[9]

Dermatologic Adverse Effects

Epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the denosumab group compared to the placebo group in the FREEDOM trial.[16]

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing.[9] There were no observed cases of ONJ in the FREEDOM trial.[16] ONJ has been reported in patients receiving denosumab. In 2 clinical trials comparing denosumab with zolendronate for the treatment of bone metastases in patient with cancer, ONJ occurred in 1.5% of the denosumab treated patients compared with 1.3% of zolendronate treated patients (p=NS).[25] The package insert recommends a dental examination with appropriate preventive dentistry prior to treatment in patients with risk factors for ONJ such as invasive dental procedures, diagnosis of cancer, poor oral hygiene,

Table 6 | Ongoing denosumab studies.

Clinicaltrials.gov Identifier	Description
NCT01077154	Adjuvant for women with high risk early breast cancer receiving neoadjuvant or adjuvant therapy
NCT00896454	Hypercalcemia of malignancy
NCT00980174	Males with osteoporosis
NCT00095498	Rheumatoid arthritis
NCT00396279	Recurrent or unresectable giant cell tumor of bone
NCT00330759	Bone metastases in advanced cancer or multiple myeloma
NCT00089674	Bone loss with androgen-deprivation therapy for non-metastatic prostate cancer
NCT00556374	Breast cancer receiving aromatase inhibitor therapy

Table 7 | Adverse events of denosumab in the FREEDOM trial.[16]

Event	Denosumab (N=3886)	Placebo (N=3876)	P Value
All	3605 (92.8)	3607 (93.1)	0.91
Serious	1004 (25.8)	972 (25.1)	0.61
Fatal	70 (1.8)	90 (2.3)	0.08
Leading to study discontinuation	93 (2.4)	81 (2.1)	0.39
Leading to discontinuation of study drug	192 (4.9)	202 (5.2)	0.55
Adverse events			
Infection	2055 (52.9)	2108 (54.4)	0.17
Cancer	187 (4.8)	166 (4.3)	0.31
Hypocalcemia	0	3 (0.1)	0.08
Osteonecrosis of the jaw	0	0	NA
Serious adverse events			
Cancer	144 (3.7)	125 (3.2)	0.28
Infection	159 (4.1)	133 (3.4)	0.14
Cardiovascular event	186 (4.8)	178 (4.6)	0.74
Stroke	56 (1.4)	54 (1.4)	0.89
Coronary Heart Disease	47 (1.2)	39 (1.0)	0.41
Peripheral Vascular Disease	31 (0.8)	30 (0.8)	0.93
Atrial Fibrillation	29 (0.7)	29 (0.7)	0.98
Adverse events occurring in at least 2% of subjects			
Eczema	118 (3.0)	65 (1.7)	<0.001
Falling	175 (4.5)	219 (5.7)	0.02
Flatulence	84 (2.2)	53 (1.4)	0.008
Serious adverse events occurring in at least 0.1% of subjects			
Cellulitis (including erysipelas)	12 (0.3)	1 (<0.1)	0.002
Concussion	1 (<0.1)	11 (0.3)	0.004

and several others.

Suppression of Bone Turnover

Reductions in bone formation markers (i.e., osteocalcin and procollagen type 1 N-terminal peptide [PlNP]) were observed starting 1 month after the first dose of denosumab. After discontinuation of denosumab therapy, markers of bone resorption increased to levels 40-60% above pretreatment values but returned to baseline levels within 12 months.[9]

In the FREEDOM trial, denosumab resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover (CTX-I, TRAP-5b, and P1NP) compared with placebo.[16] After 36 months, a little more than one-third of patients treated with denosumab had clinical signs of suppressed bone formation compared with no patients who received placebo. The significance of these findings and the effect of long-term treatment with denosumab are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with denosumab may contribute to adverse outcomes such as ONJ atypical fractures, and delayed fracture healing.[9]

Annual Cost

Fosamax®, Miacalcin®, and Fortical® are the only products on the market with FDA approved generic alternatives. Only alendronate 70mg and 35mg tablets are available at Wal-mart for $9 per month or $24 per 3 month supply. The most expensive FDA-approved medication to treat osteoporosis currently on the market is Forteo® at $11,379.24 annually. The majority of osteoporosis treatments range from $857 (Fosamax® 10mg daily) to $1650 (Prolia® 60mg Q6M) annually (**Table 8**).

Table 8 | Annual cost of FDA-approved osteoporosis treatments.[26]

Treatment	Dosage	Annual Cost (USD)
Bisphosphonates		
Alendronate (Fosamax®)	70 mg once/week	355.88 (96.00[a])
	10 mg once/daily	857.75
Alendronate / cholicalciferol (D3) (Fosamax Plus D®)	70mg / 2800mg once/week	1236.12
	70mg / 5600mg once/week	1221.84
Ibandronate (Boniva®)	150 mg once/month	1394.60
	2.5 mg once/daily	1404.00
	3mg/3mL once/3 months	1897.48
Risendronate (Actonel®)	5 mg once/daily	1493.16
	35 mg once/week	1433.16
	150 mg once/month	1507.44
Risendronate / calcium carbonate (Actonel with Calcium®)	35mg once/wk; 1250mg on 6 days/wk	1366.08
Zoledronic acid (Reclast®)	5mg/100 mL once/year	1137.19
Monoclonal Antibody		
Denosumab (Prolia®)	60mg/ml once/6 months	1650.00
Calcitonin		
Calcitonin-salmon (Miacalcin®, Fortical®)	200 mcg IN once/daily (alternating)	899.88
	100 units IM/SQ once/every other day	5341.56
Selective estrogen receptor modulator (SERM)		
Raloxifene (Evista®)	60 mg once/daily	1586.16
Recombinant parathyroid hormone		
Teriparatide (Forteo®)	20 mcg SQ once/daily	11379.24

Cost of one year's treatment for the drug alone, based on September 21, 2010 data from www.drugstore.com. Costs are for generic medications if available.
[a] Estimated Wal-Mart cost.

SUMMARY

Osteoporosis is a common skeletal disease associated with an imbalance in bone remodeling resulting in a reduction in bone strength and increased fracture risk. A major regulator of osteoclastic bone resorption is RANKL. The binding of RANKL to its receptor (RANK) increases the formation, activity, and survival of osteoclasts. Prolia® (denosumab) prevents RANKL from binding to RANK thereby reducing the formation, activity, and survival of osteoclasts. In women with PMO, denosumab 60 mg by subcutaneous injection every 6 months increased bone mineral density (BMD), reduced bone turnover markers, and reduced the risk of vertebral, hip, and non-vertebral fractures. Denosumab has been well tolerated with a safety profile generally similar to placebo. Denosumab may be useful in clinical practice for the treatment of PMO in women with GI contraindications, side effects, or malabsorption to oral bisphosphonates.

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