Osteoporosis Primary Prevention and Treatment: care gaps and impact of COVID-19 on assessment and treatment

Prof. N Harvey

Prof. E McCloskey

Dr J Blanch-Rubió

HOUSEKEEPING

Anyone can submit questions for the Q&A

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This webinar is being recorded

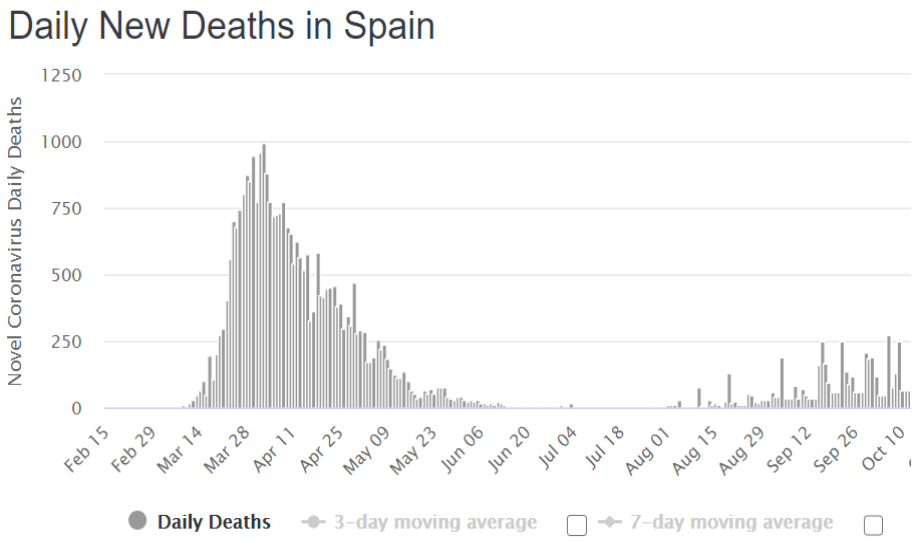
Influence of anti-osteoporosis treatments on the incidence of COVID-19 in patients with non-inflammatory rheumatic conditions

Dr. Josep Blanch-Rubió
Section Head, Rheumatology Service, Hospital del Mar
Barcelona, Spain

Reference:
Blanch-Rubió J, Soldevila-Domenech N, Tío L, Llorente-Onaindia J, Ciria-Recasens M, Polino L, Gurt A, de la Torre R, Maldonado R, Monfort J, COVIDMAR Study Group. Influence of anti-osteoporosis treatments on the incidence of COVID-19 in patients with non-inflammatory rheumatic conditions. Aging (Albany NY). 2020 Oct 20;12(20):19923-19937. doi: 10.18632/aging.104117.

COVID-19 pandemics in Spain

Spain has suffered one of the **highest rates of COVID-19 incidence and deaths in Europe**, mostly between **March and April 2020**[1,2]

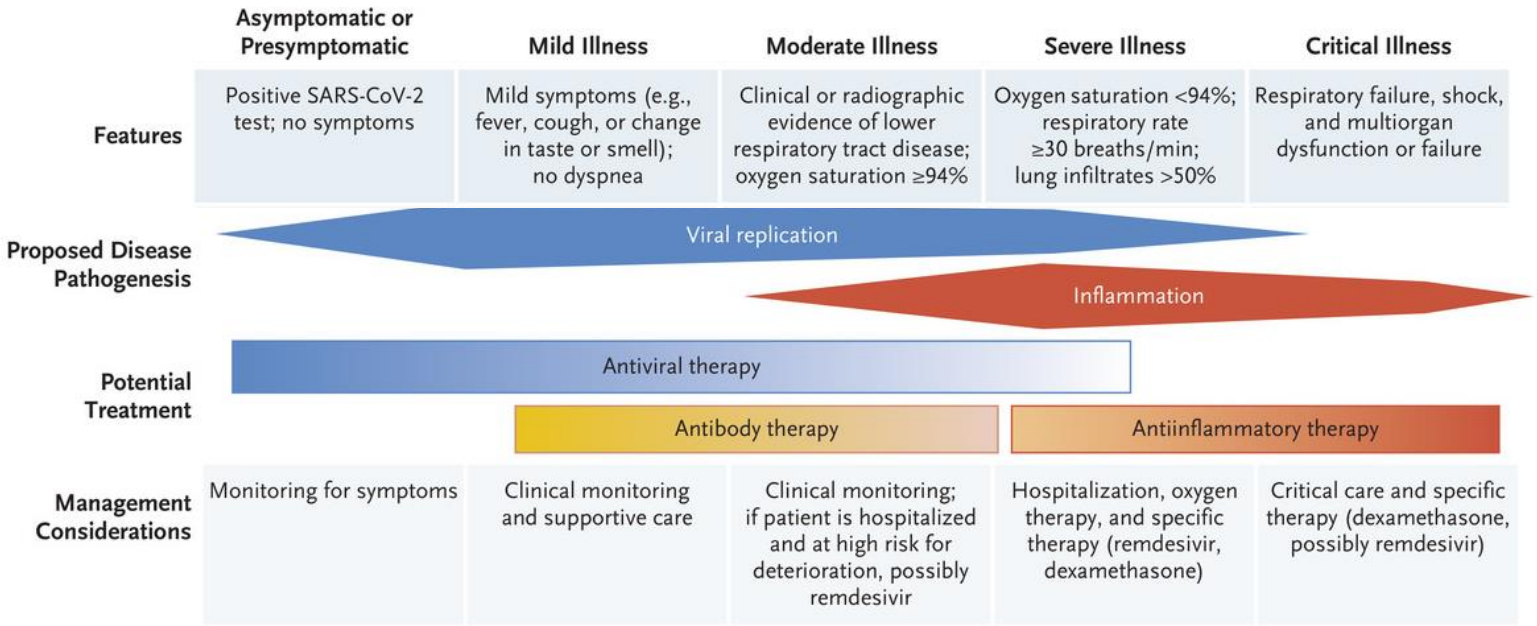


3 May 2020

Reporting Country/ Territory/Area	Total confirmed cases	Total deaths
Europe		
Spain	216582	25100
Italy	209328	28710
The United Kingdom	182264	28131
Germany	162496	6649
Russian Federation	134687	1280
France	129458	24724
Turkey	124375	3336

[1]Worldometer: Coronavirus. [2]WHO – Coronavirus: Situation report – 104 (3 May 2020)

COVID-19 progression and Inflammation



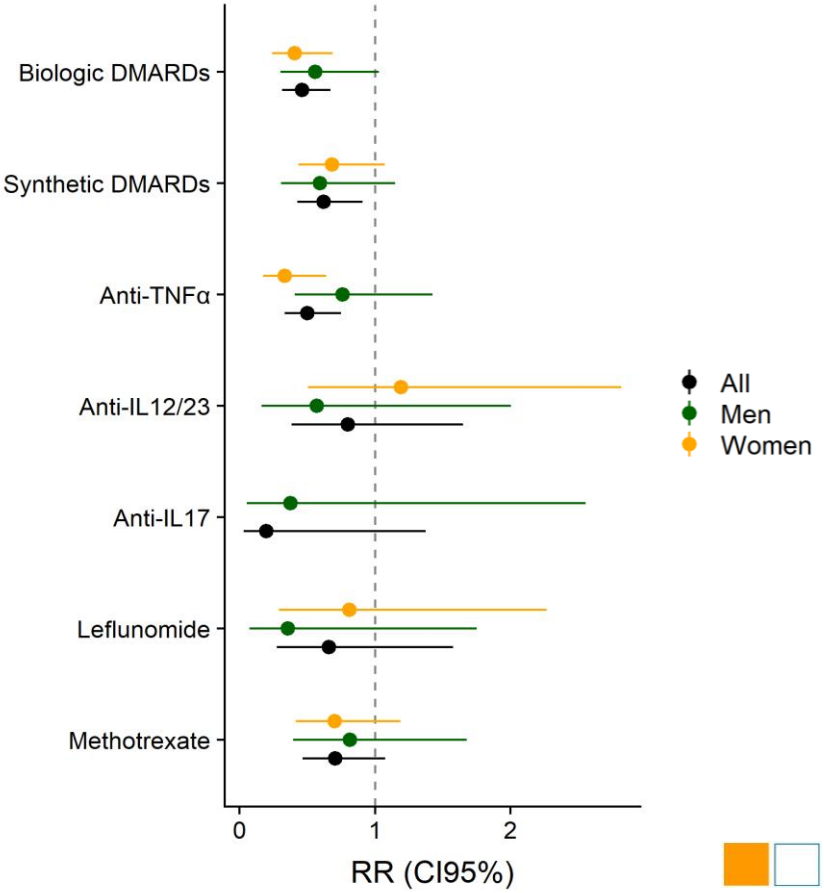
The **immune system** seems to be **dysregulated** in severe forms of COVID-19, probably due to abnormal responses by monocytes, macrophage, and/or dendritic cells[3,4]

[3]Gandhi RT et al. N Engl J Med 2020; Oct(29); 383:1757-1766. [4]Merad M, et al. Nat Rev Immunol. 2020 Jun;20(6):355-362.

DMARDs and COVID-19

Potential **protective effects** of some disease-modifying, anti-rheumatic drugs (**DMARDs**) to treat COVID-19 (some are currently used off-label)

Our team[5] and other researchers[6] have also shown that some of these **anti-rheumatic treatments could reduce COVID-19 incidence**

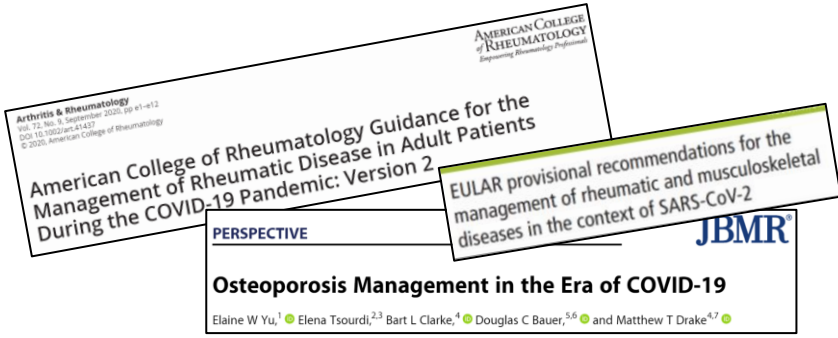


[5]Soldevila-Domenech N, Tío L, Llorente-Onaindia J, Martín-Garcia E, Nebot P, de la Torre R, Gurt A, Maldonado R, Monfort J, COVIDMAR Study Group. COVID-19 incidence in patients with immunomodulated inflammatory diseases: Influence of immunosuppressant treatments. Frontiers in Pharmacology (PROVISIONALLY ACCEPTED).
[6]Michelena X, et al. Semin Arthritis Rheum. 2020; 50:564–70.

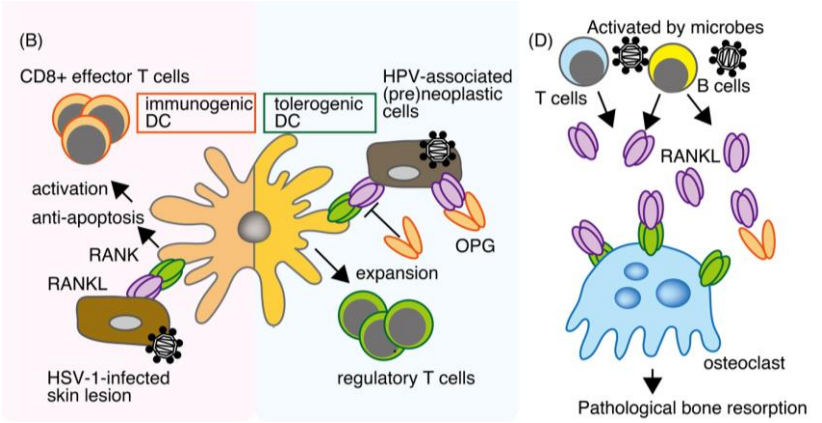
Justification of the study

The possible effects of **anti-osteoporosis treatments** in the **clinical expression** and **incidence of COVID- 19 remained un-known**

Positive impact for patient prognosis



Since the RANK-L system is involved in processes related to the immune system[7,8], we hypothesized that **Denosumab** (fully human monoclonal antibody against RANK-L that inhibits osteoclastogenesis) **could modulate the immune response** associated to SARS-CoV-2



[7]Cheng ML, et al. Front Oncol. 2014; 3:329.
[8]Kobayashi-Sakamoto M, et al. Integr Mol Med. 2015; 2:384–90.

Methods

OBJECTIVE

To elucidate the possible effects of **anti-osteoporosis drugs** (anti-resorptives, calcium and vitamin D) and **associated treatments** (analgesics and antidepressants) on **COVID-19 incidence and clinical expression**

POPULATION [2102]

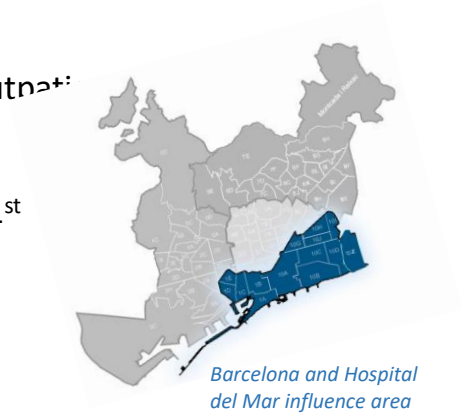
Patients with **osteoporosis, osteoarthritis and/or fibromyalgia**, living in the influence area of a referral hospital in Barcelona and receiving care at the outpati Rheumatology Service for the last 6 months

DESIGN

Cross-sectional study of the cumulative incidence of COVID-19 from March 1st to May 3rd 2020. Hospital and primary care clinical history revision was performed

OUTCOME

COVID-19 diagnosis



Barcelona and Hospital del Mar influence area

ANALYSES

Cumulative age-standardized incidence rate of COVID-19 in the study population for comparisons with the general population of Barcelona
Multivariable-adjusted Poisson regression models to evaluate associations between different treatments and the presence of COVID-19

Population characteristics

2102 **Individuals**

80.5%	Women
66.4	years old
63.7%	Osteoarthritis
43.5%	Osteoporosis
27.2%	Fibromyalgia
42.4%	Hypertension
15.0%	Pulmonary disease
14.9%	CV disease
12.6%	Diabetes
12.6%	Denosumab
8.5%	Intravenous Zoledronate
6.8%	Oral bisphosphonates
23.3%	Calcium
62.0%	Vitamin D
12.5%	Thiazide diuretics
58.0%	Analgesics
31.3%	Antidepressants

109 COVID-19 diagnosis

Crude cumulative incidence rate = **5.2% (CI95% 4.2-6.1%)**

Grade

57.8%	Mild
14.7%	Moderate
27.5%	Severe

Evolution

65.1%	Home
22.9%	Hospitalization
2.8%	NIV
0.9%	ICU
8.3%	Death

Cumulative age-standardized incidence rate of COVID-19

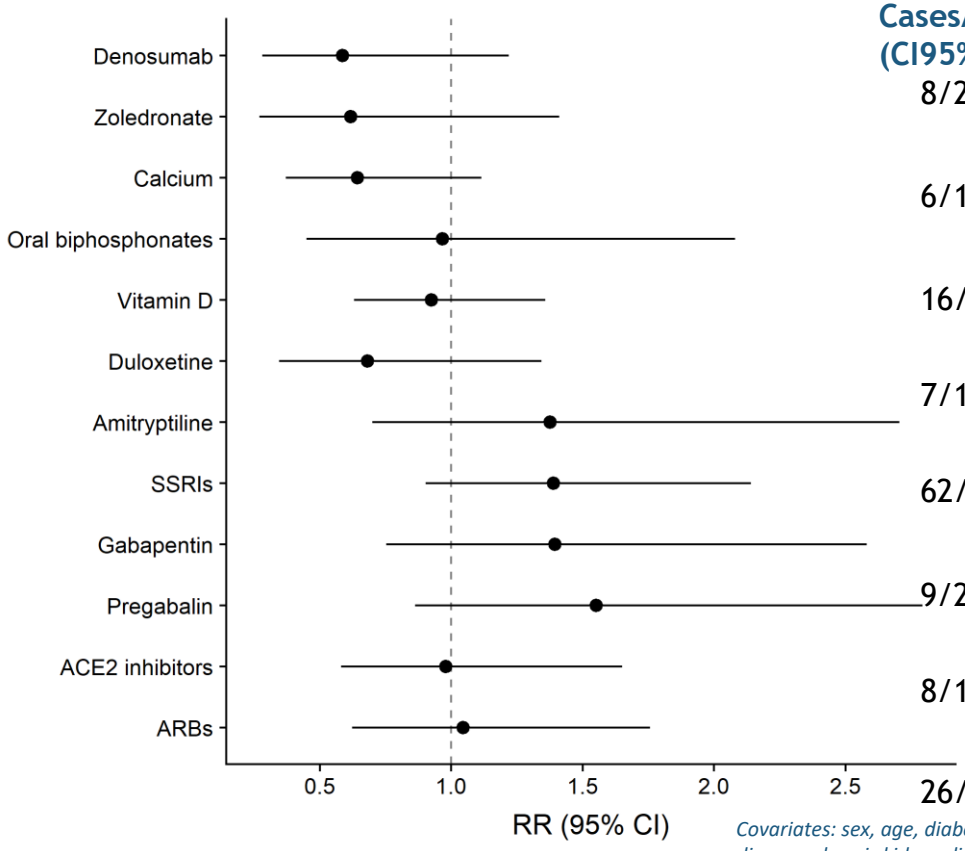
General population of Barcelona:
3.69%
(3.66-3.73%)

Study population

Osteoporosis:	2.98% (1.88-4.08%)	↓
Osteoarthritis:	4.58% (3.46-5.70%)	↑
Fibromyalgia:	4.45% (2.76-6.14%)	↑

No significant differences

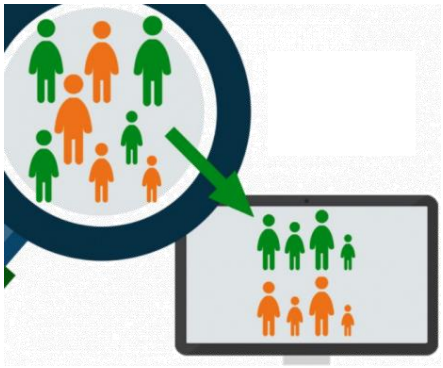
Adjusted relative risk (RR) of COVID-19



	Cases/Exposed (CI95%)	RR
Denosumab	8/264	0.58 (0.28, 1.22)
Zoledronate	6/179	0.62 (0.27, 1.41)
Calcium	16/490	0.64 (0.37, 1.12)
Oral biphosphonates	7/143	0.97 (0.45, 2.08)
Vitamin D	62/1303	0.92 (0.63. 1.36)
Duloxetine	9/207	0.68 (0.34, 1.34)
Amitryptiline	8/102	1.38 (0.70, 2.71)
SSRIs	26/333	1.39 (0.90, 2.14)
Gabapentin	11/164	1.39 (0.75, 2.58)
Pregabalin	12/146	1.55 (0.86, 2.79)
ACE2 inhibitors		
ARBs		

Covariates: sex, age, diabetes, pulmonary disease, cardiovascular disease, chronic kidney disease, and active cancer or treatment.

Propensity score matching



In the population with **osteoporosis**, each treated individual with **denosumab**, **bisphosphonates** and **calcium** was matched with an untreated individual with similar characteristics (sex, age, cardiovascular disease, diabetes, pulmonary disease, kidney disease and cancer).

Almost equivalent estimates were obtained:

Denosumab: RR=0.73 (0.30, 1.78)
Zoledronate: RR=0.55 (0.20, 1.44)
Calcium: RR=0.72 (0.39, 1.37)

Discussion of main findings

The exposure to **denosumab, intravenous zoledronate** and **calcium** were associated with **30-40% decreased risk of COVID-19** in the study population. Potential mechanisms:

- RANK-L inhibition by **denosumab** modifies immune cell profiles and **decreases the activity of pro-inflammatory cytokines**[8] → might elicit beneficial effects during viral infections and could attenuate the hyperactivity of pro-inflammatory cytokines associated with COVID-19 progression

- **Zoledronate** may make **dendritic cells** and their precursors **less susceptible to SARS-CoV-2 infection**. It inhibits the prenylation of small GTPases, which may hinder endosomal exocytosis in the dendritic cells required for the advance of SARS-CoV-2 infection[9]

- **Calcium** supplements may counteract the decreased serum levels of calcium promoted by SARS-CoV-2 infection, which may lead to an **improvement of the immune cell response** and attenuate the probability of infection progression[9,10]

[8]Kobayashi-Sakamoto M, et al. Integr Mol Med. 2015; 2:384–90. [9]Brufsky A, et al. J Transl Med. 2020; 18:261. [9]Cappellini F, et al. Clin Chem Lab Med. 2020; 58:e171–73. [10]Vaeth M, et al. Immunity. 2016; 44:1350–64.

LIMITATIONS

No information on **osteoporosis grade**

Potential **confounding by indication**
(when the clinical indication for selecting a particular treatment also affects the outcome)

Cross-sectional design
Data collected by many medical researchers or clinicians that reviewed the medical history

We included patients from a tertiary hospital with probably **more severe forms of non-inflammatory rheumatic conditions**

COVID-19 Asymptomatic patients not detected

STRENGTHS

Similar RR estimates after Propensity Score Matching

Large sample size (N=2102)
Several meetings among researchers to **unify classification criteria**

All medications covered by the public health insurance system in Spain, thus **avoiding differences related to medication costs**

Conclusions

The main treatments currently used for osteoporosis are not associated with an increase in COVID-19 incidence

In contrast, a **decreased incidence of COVID-19** was revealed with two anti-resorptives drugs, denosumab and zoledronate, as well as with calcium treatment.

Some of the pain treatments used in these non-inflammatory rheumatic conditions **may influence COVID-19 outcomes**, since the incidence of COVID-19 was decreased in patients treated with duloxetine and increased in those taking pregabalin.

In conclusion, our data are consistent with a **lack of direct relationship between osteoporosis therapies and COVID-19 incidence**, providing scientific evidence in support of the recently-published guidelines by the ACR, EULAR, ASBMR and IOF[11-14] to maintain anti-osteoporosis treatments for COVID-19 patients, which were based solely on expert opinions.

[11]American College of Rheumatology COVID-19 Guidance Task Force. COVID-19 Clinical Guidance for Patients with Rheumatic Diseases. Am Coll Rheumatol. 2020; 1–2.
[12]Landewé RB, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis. 2020; 79:851–58.
[13]ASBMR webinar panel on treating patients with osteoporosis during the COVID-19 pandemic [Internet]. 2020.
[14]Yu EW, et al. Osteoporosis management in the era of COVID-19. J Bone Miner Res. 2020; 35:1009–13

THANK YOU!

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Q&A

IOF International Osteoporosis Foundation

Thank you

On behalf of IOF, we thank you for your participation in this webinar

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