Annex

Studies that support the usefulness of chondroprotectors.

According to Dr. Miguel Bernad, specialist in Rheumatology at the University Hospital La Paz in Madrid: "In recent decades, there have been many studies, systematic reviews and meta-analysis related to osteoarthritis and the use of such drugs, some of which have resulted in contradictory findings.

It is important, when evaluating these publications, to take into account the methodologies employed and the type of studies on which they are based, since they may have an influence on the production of biased conclusions".

In **2010**, **Wandel** published a meta-analysis in the BMJ in which he concluded that CS and G had no positive effect on patients with osteoarthritis, which was somewhat surprising given the evidence to date and the clinical experience indicating significant improvements in a significant proportion of patients with pain secondary to osteoarthritis. This publication has been used by health managers to limit the prescription of these drugs and has led to the non-application of certain Therapeutic Guidelines. In any case, the CS and the G, alone or in association, are strongly recommended (Grade of evidence A and Grade of recommendation 1) in guides as important domestically as SEMFYC, SEMERGEN, SER and SECOT, and internationally as EULAR, ESCEO and PANLAR.

In recent years, three important studies have been published that refute Wandel's results.

In **2015**, the MOVES study was published, a multinational clinical trial (Germany, France, Poland and Spain) on an anti-inflammatory drug, including more than 600 patients and lasting for 6 months. It was shown that the symptomatic improvement in osteoarthritis pain is similar in the group of patients taking CS + G as in those taking the anti-inflammatory Celecoxib.

The **MOSAIC** study published in 2016 in Canada by Pelletier includes randomized, double-blind trials with almost 200 patients for 2 years, comparing CS versus the anti-inflammatory Celecoxib. The conclusions are that the symptomatic improvement is similar in both groups and that the group treated with CS showed a significant reduction of cartilage deterioration in the knee when verified by NMR with respect to the group treated with the anti-inflammatory. Therefore, we can talk about the symptomatic effect and structural effect of CS.

In 2017, Register published the multinational, randomized, double-blind **CONCEPT** study, which compares the treatment with CS, the anti-inflammatory Celecoxib and placebo in more than 600 patients with knee osteoarthritis, concluding that patients receiving active medication (CS and Celecoxib) registered significant improvements in terms of pain and functionality with respect to the placebo group.

Finally, during the last year a Delphi study was published by OAFI (Osteoarthritis Foundation International), in which a group of expert panelists confirm the benefit and indications of chondroprotectors (SYSADOAS) in the treatment of osteoarthritis.

About other treatments with NSAIDs, paracetamol and opioids

Other treatments such as Paracetamol, NSAIDs and opioids have an exclusively symptomatic effect while they are being used and are prone to producing side-effects with a far greater frequency than chondroprotectors.

Patients with osteoarthritis may live more than 30 years with the disease; however, the therapeutic arsenal available to treat this chronic and degenerative disease is very limited. Currently, the pharmacological coverage provided by the NHS's pharmaceutical treatment is limited to SYSADOAs, analgesics (including opioids) and NSAIDs. However, numerous studies warn that the long-term use of analgesics and NSAIDs by patients with osteoarthritis could lead to significant additional health problems, as they are mostly polymedicated and comorbid. Hence the need to follow treatments with SYSADOAs to improve the quality of life of patients.

There is much scientific evidence about the side effects of Paracetamol, with a 2019 Cochrane review concluding that there are no clinical benefits derived from its use.

Analgesics have a very limited role in the treatment of osteoarthritis, as the disease has a significant inflammatory component that limits the effectiveness of such drugs. The latest Cochrane review of paracetamol reaches this conclusion, stating that the drug does not offer clinically significant benefits in this population. In terms of their safety profile, analgesics are not exempt from adverse effects, as demonstrated through clinical practice, and contrary to SYSADOAs they may not be used long-term.

Regarding **NSAIDs (anti-inflammatories)**, the possibility of side effects at the cardiovascular (AMI and Stroke), digestive, hepatic and/or renal levels are very high, and more so in the target population subject to this pathology, which is usually composed of people over 65 years of age with other concomitant risk factors and pathologies and who are polymedicated. As such, analgesics are not recommended at all.

Opioids are not suitable analgesics for the treatment of osteoarthritis, but in the face of moderate or severe chronic pain they are nevertheless being used with positive short-term results, although with significant safety problems in terms of tolerance and dependence.

Therefore, given the limited alternatives in terms of therapeutic drug treatment, chondroprotectors take on a special relevance for doctors and patients. This is long-term medication, which has been clinically proven to reduce pain, stiffness, and which has a positive safety profile.

Budget impact report with chondroitin versus NSAIDs (anti-inflammatories)

We next analyze the **data extracted from the Health and Economic Impact Report on Chondroitin Sulfate (CS) chondroprotection, prepared by the consultancy Health Value and directed by Carlos Rubio Terrés, an expert in pharma-coeconomics** (see attached CV).

The data show the health savings represented by chondroprotection for the National Health System as a result of the **avoidance of gastrointestinal adverse effects (GIAE), coronary ischemic events (CIE), acute (AKI) and chronic (CKI) kidney injury, in comparison with non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 inhibitors (COXIBs)**.

Similarly, the health costs derived from the use of anti-inflammatory drugs in patients with knee osteoarthritis have been quantified, assuming that they have displaced the treatment with Sysadoas. That is to say, a de-financing scenario has been simulated, with the fall in the prescription of Sysadoas being replaced by anti-inflammatories.

In this scenario, the cost would be extremely high, increasing the expenditure of the NHS by **21.8** million euros, derived from the high cost of managing the adverse effects associated with anti-inflammatory drugs (the estimated cost of a serious gastrointestinal RA is almost € 3,000, heart disease costs more than € 6,000 and a chronic kidney injury costs more than € 10,000).

Development of the probabilistic model used

The study has been carried out on the following population:
Annual number of patients with knee osteoarthritis treated with NSAIDs: 519,000
Annual number of patients with knee osteoarthritis treated with SYSADOAs: 105,000

The data extracted are national (whole of the NHS*), have been analyzed over a period of 3 years and have had the following variables of Sysadoas vs Anti-inflammatory

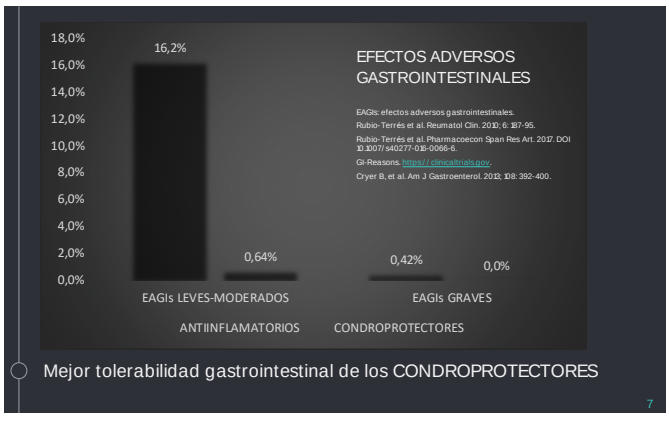
- Medication cost
- Arthrosic population in Spain
- Adverse effects cost
- Probability of adverse effects
- Toxicity saving avoided
- No. toxicity episodes avoided

*only these results are presented

And enables the calculation of:

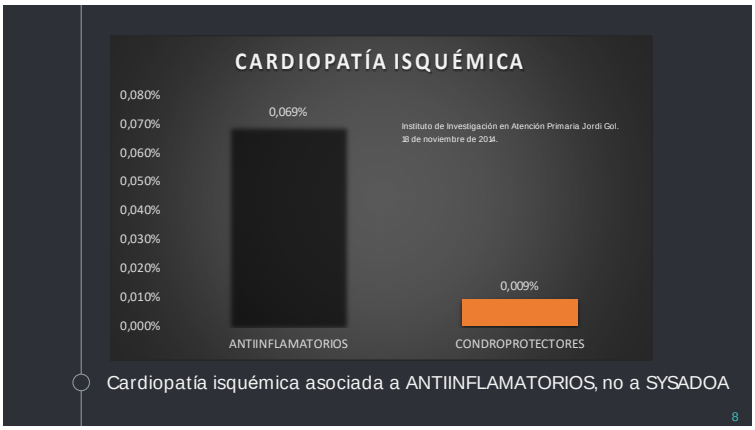
- Costs avoided with IC 95%
- Saving probability with chondroprotectors

We indicate the differences in the toxicity of the medications in order to subsequently evaluate the cost of managing the adverse effects of each group



Adverse gastrointestinal effects (AGIEs):

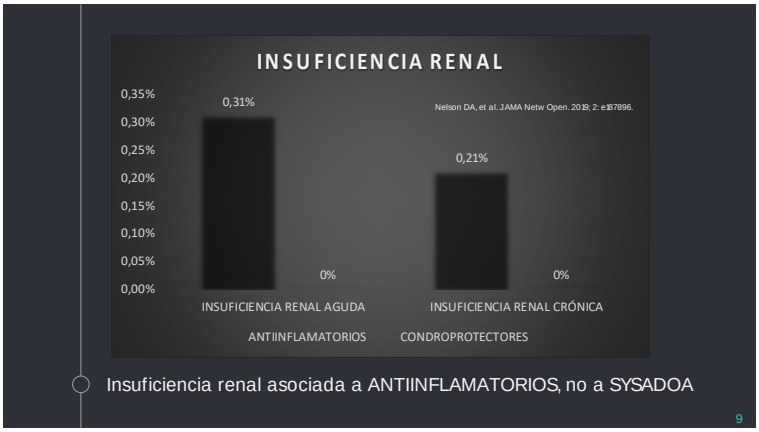
16.2% with anti-inflammatories
0.64% with chondroprotectors



Ischemic heart disease:

0.069% with anti-inflammatories versus

0.009% with chondroprotectors



Kidney failure:

acute 0.31%
chronic 0.21%
with anti-inflammatories

Not described with chondroprotectors

Adverse effect costs

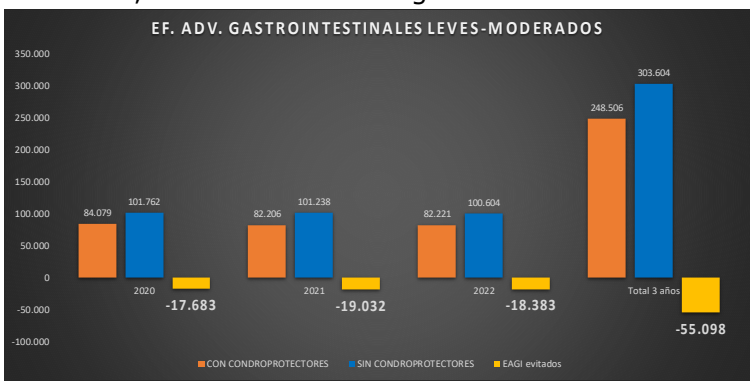
Cost of each adverse effect:

AGIEs SLIGHT-MODERATE: € 240
EAGLIs serious: € 2,857
Ischemic heart disease: € 6,168
Acute kidney failure: € 6,011
Chronic insufficiency: € 10,221

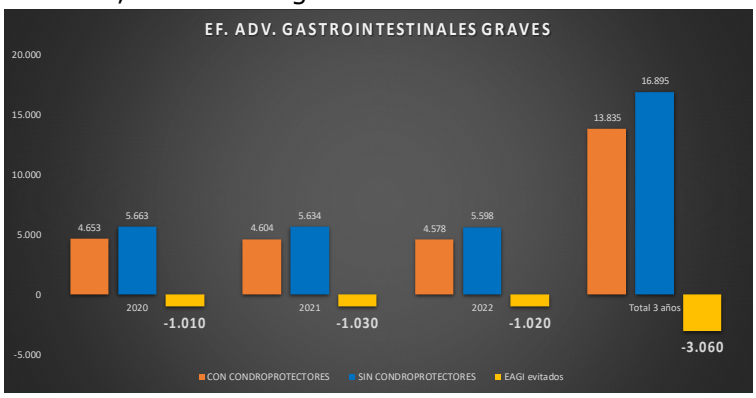
Results

- **In the 3-year period, the following episodes of adverse events would be avoided with the use of chondroprotectors:**

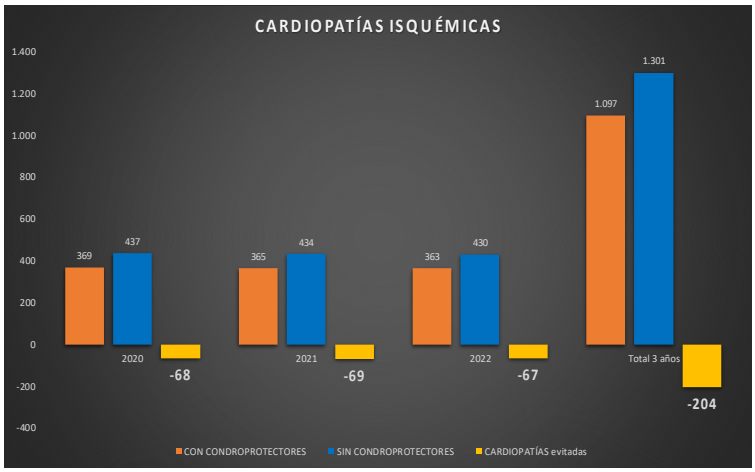
  - 55,098 mild-moderate gastrointestinal effects



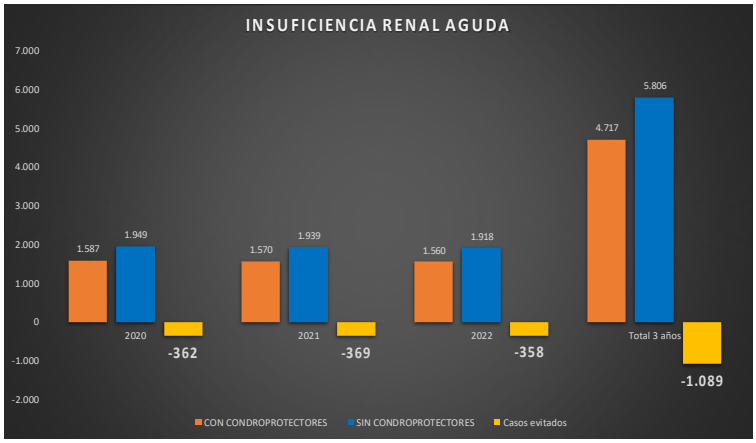
  - 3,060 serious gastrointestinal effects



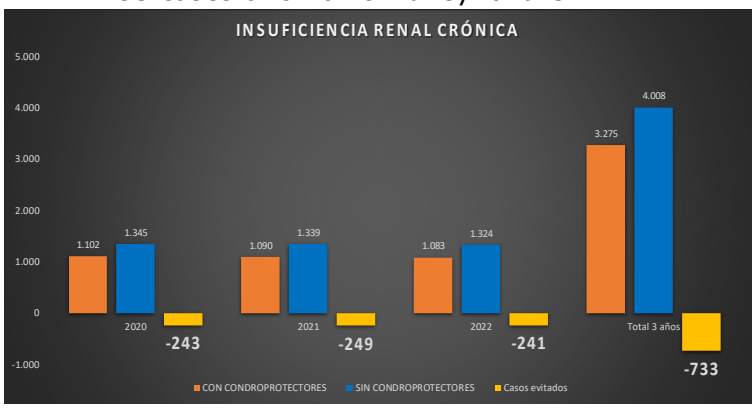
  - 204 ischemic heart disease



- 1,089 cases of acute kidney failure



- 733 cases of chronic kidney failure



- **The savings from the avoidance of adverse effects through the use of chondroprotectors would be 40.9 MILLION EUROS OVER 3 YEARS** (contemplating only the cost of toxicities, not the cost of medicines)