Effects of Intramuscular Sodium Ribonucleinate (Osteochondrin® S) in Osteoarthritis of the Knee: Identification of 'Responders' and 'Non-responders'

K D Rainsford[1], W W Bolten[2], K-H Schuehlein[3], A Dempsey[3], J Schnitker[4]

[1] Biomedical Research Centre, Sheffield Hallam University, Sheffield, United Kingdom, [2] Rheumatologie, Klaus-Miehlke-Klinik, Wiesbaden, [3] Dyckerhoff-Pharma GmbH, Köln, [4] Insitut für angewandte Statistik GmbH, Bielefeld, Germany

Introduction

Osteochondrin® S (OST) is a natural ribonucleotide extract of connective tissues and yeast which has been shown to have benefit in several animal models of joint injury and in small scale trials in patients with osteoarthritis (OA) (Rainsford, K.D.). The action of OST has been ascribed to effects on the enhanced stimulation of pathologically depressed cell activity and improvement of the regeneration of impaired tissue.

The treatment with IOST involves administration of a series of 20 intramuscular injections over a period of 4 weeks which, as a rule, will be repeated after some months. About 2 weeks after beginning the therapy, according to 8-12 ampoules Osteochondrin® S, increased cell activity will be noticed by lessening of the patients complaints. The peak of efficacy will be reached in about 8-12 weeks after the end of injections, what suggests repeating the series about 3 months after the end of the series before in order to benefit from cumulative effects.

The efficiency of Osteochondrin® S for the treatment of degenerative diseases of the locomotion system has been demonstrated previously in several trials but these do not comply with present day ICH guidelines for Good Clinical Practice.

Study Objectives

To determine the efficacy of OST compared with placebo (PLA) for the treatment of pain and joint stiffness components of the WOMAC Index, and the relief of pain assessed by the intake of ibuprofen as a rescue medication.

Study Design

Prospective, randomised, double-blind, parallel, placebo controlled phase III multi-centre trial in patients with radiologically-established osteoarthritis of the knee (gonarthritis). The patients were included if they had

- Pain in the knees for at least half of the days in the preceding 2 months before the trial
- Aged between 40 and 75 years
- WOMAC Indices for PAIN ≥ 200 as the sum of the 5-point pain Visual Analogue Scale (VAS) **and** for JOINT STIFFNESS ≥ 80 as the sum of the 2 stiffness VAS parameters

Methods and Treatment Schedules

The study was performed according to the ICH GCP guidelines. Initially 168 patients were enrolled with the study in a two arm treatment design.
The flow diagram in Figure 1 shows the overall organisation of the treatment schedule.

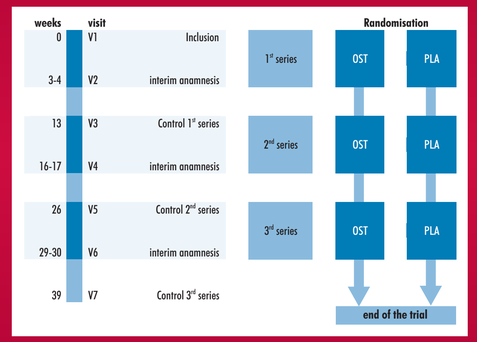

Figure 1: Treatment and observation assessments

Statistical Assessments

The primary measure was the O'Brien rank sum of the changes from baseline in the dimensions, pain and joint stiffness of the WOMAC index (Dougados, M. et al.) after 3 months and the need of analgetic/antiphlogistic rescue medication (Ibuprofen) in the follow-up period of the first quarter.

With the recent development of OARSI of 'responder' and 'non-responder' criteria for studies in osteoarthritis (Dougados, M. et al.), these criteria were applied to the WOMAC pain and joint stiffness criteria as shown below.

For scales of range 0 to 100, the limits
high improvement in pain: ≥30
moderate improvement in pain: 10 – <30
moderate improvement in function: ≥20
were used.

For the patient global assessment, moderate improvement was represented by the scores 'moderate' to 'very good'.
moderate improvement in patient global assessment: moderate, good, very good.

The range 0 – 50 of WOMAC dimension pain, and 0 – 170 of WOMAC dimension physical function, resp., yield the limits
high improvement in pain: ≥15
moderate improvement in pain: 5 – <15
moderate improvement in function: ≥34

which finally were used for the assessment of response.

The responders excepting the OARSI Responder Criteria Proposition A are defined as improvement ≥ 20% for the WOMAC total index and subscales.

Results

The outcome of patients entering and then completing the study is shown in Table 1.

Patients	OST	PLA	All patients
Number of patients	84	82	166
Safety Analysis	**84 (100.0%)**	**82 (100.0%)**	**166 (100.0%)**
Early termination not related to efficacy	4 (4.8%)	1 (1.2%)	5 (3.0%)
Exclusion of centre no. 17	4 (4.8%)	4 (4.9%)	8 (4.8%)
Exclusion of centre no. 21	4 (4.8%)	4 (4.9%)	8 (4.8%)
Full Analysis Set	**72 (85.7%)**	**73 (89.0%)**	**145 (87.3%)**
Major protocol violations (with FAS)	12 (14.3%)	13 (15.9%)	13 (15.9%)
Valid Case Set	**60 (71.4%)**	**60 (73.2%)**	**60 (73.2%)**

Table 1: Disposition of patients completing the study

Table 2 shows the overall data for the Total WOMAC Index, Pain, Stiffness and Physical Function Scales from the patients that completed the PLA and OST treaments. The results show that for all the patients there was a statistically significant difference ($P<0.05$) between the two treatments for WOMAC Index as well as the Pain and Physical Function Scales, but not for the Stiffness Scale.

Variable	OST	PLA	U test: p values one-sided
Total index	-636.2	-506.7	p=0.0270
Pain scale	-146.3	-118.4	p=0.0426
Stiffness scale	-60.3	-53.3	p=0.2012
Physical function scale	-429.7	-335.1	p=0.0265

Table 2

A relatively high placebo reactor rate was observed. Using a responder criterion for classification of 'responders' from 'non-responders' the following data was obtained for responders rates (Table 3).

Variable	OST	PLA	χ^2 test	REGRESSION
Total index	88.3%	65.0%	p=0.0013	p=0.0024
Pain scale	88.3%	70.0%	p=0.0067	p=0.0046
Stiffness scale	90.0%	75.0%	p=0.0153	p=0.0204
Physical function scale	85.0%	65.0%	p=0.0057	p=0.0075
OARSI responder rate	88.3%	71.7%	p=0.0113	p=0.0122

Table 3

The superiority was proven on the basis of both methods (X^2 test, regression) and 4 variables simultaneously. Figure 2 shows the disposition of "responder" and "non-responder" patients in the full analysis according to the OARSI critera. OST showed superior efficacy over PLA but because of high placebo reactor rates this was more effective in the evaluation with a responder criterion.

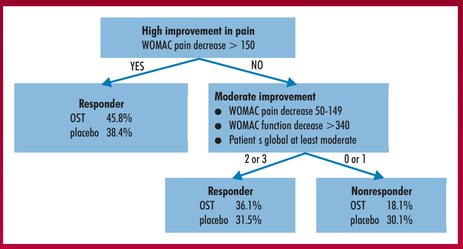

Figure 2: Responders in the full analysis set according to OARSI criterion - proposition A (p=0.0446 one-tailed)

Conclusion

Osteochondrin®S showed superior efficacy compared with placebo but there were a high proportion of placebo responders. Consequently, this drug was found more effective in patients defined as 'responders' compared with 'non-responders' when assessed according to the OARSI criteria.

Key References

Dougados M et al. Response criteria for clinical trials on osteoarthritis of the knee and hip in Oesteoarthritis and Cartilage (2000) 8, 395-403

Rainsford KD (1996) Mode of action, uses, and side effects of anti-inflammatory drugs. In Rainsford, K.D. (Ed). Advances in Anti-Rheumatic Therapy. CRC Press, Boca Raton, pp. 59-111

Sheffield Hallam University