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An integrated analysis of five double-blind, randomized controlled trials evaluating the safety and efficacy of a hyaluronan product for intra-articular injection in osteoarthritis of the knee[1]

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Summary

Objective: Five double-blind, randomized, saline-controlled trials (RCTs) were included in the United States marketing application for an intra-articular hyaluronan (IA-HA) product for the treatment of osteoarthritis (OA) of the knee. We report an integrated analysis of the primary Case Report Form (CRF) data from these trials.

Method: Trials were similar in design, patient population and outcome measures – all included the Lequèsne Algofunctional Index (LI), a validated composite index of pain and function, evaluating treatment over 3 months. Individual patient data were pooled; a repeated measures analysis of covariance was performed in the intent-to-treat (ITT) population. Analyses utilized both fixed and random effects models. Safety data from the five RCTs were summarized.

Results: A total of 1155 patients with radiologically confirmed knee OA were enrolled: 619 received three or five IA-HA injections; 536 received "placebo" saline injections. In the active and control groups, mean ages were 61.8 and 61.4 years; 62.4% and 58.8% were women; baseline total Lequèsne scores 11.03 and 11.30, respectively. Integrated analysis of the pooled data set found a statistically significant reduction ($P < 0.001$) in total Lequèsne score with hyaluronan (HA) (−2.68) vs placebo (−2.00); estimated difference −0.68 (95% CI: −0.56 to −0.79), effect size 0.20. Additional modeling approaches confirmed robustness of the analyses.

Conclusions: This integrated analysis demonstrates that multiple design factors influence the results of RCTs assessing efficacy of intra-articular (IA) therapies, and that integrated analyses based on primary data differ from meta-analyses using transformed data.

Key words: Osteoarthritis, Knee, Intra-articular, Hyaluronan, Hyaluronate, Hyaluronic, Viscosupplementation, Meta-analysis.

Introduction

Intra-articular hyaluronan (IA-HA) products have been licensed in the United States for treatment of knee osteoarthritis (OA) since 1997 and in other parts of the world since 1987. For United States marketing approval, the FDA has required that IA-HA products submit evidence of safety and efficacy from double-blind, randomized controlled trials (RCTs), typically using intra-articular (IA) saline injections as the "placebo" control. Despite this standard, IA-HA treatment for knee OA continues to be controversial, primarily because trials examining this therapy have not been uniformly well-designed, yielding unimpressive results as to the magnitude and significance of active treatment compared with control[1–3].

Divergent interpretations from three recent meta-analyses have added to this controversy[4–6]. Although all report treatment effects of IA-HA compared with saline injections to be statistically significant, they differ with respect to calculated effect sizes and interpretation of clinical importance. Meta-analyses based on publications from RCTs are limited by reliance on extraction of information from summarized data and abbreviated statistics. Differing data extraction

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procedures and statistical methodology may yield disparate conclusions even when evaluating the same RCT reports. This appears especially true in meta-analyses of IA-HA RCTs, which necessarily must account for diverse trial designs, control treatments, outcome measures and evaluation time points, and data pooled across products with differing compositions and physical properties. Because hyaluronan (HA) is a natural polymer, IA-HA products can vary broadly in molecular weight and purity, and may also include synthetic crosslinks. These differences may be clinically relevant, particularly with respect to safety characteristics[7,8].

To supplement evidence provided by recent meta-analyses of IA-HA treatment, an integrated analysis of five RCTs examining a single IA-HA product is presented. Analyses were based on individual patient data from Case Report Forms (CRFs), assembled into a data set for the pooled intent-to-treat (ITT) population, and accepted by the FDA as part of a marketing application supporting a single IA-HA product[9]. This provides a comparison that avoids some limitations inherent to meta-analyses, because it circumvents the need for any type of data transformation. Importantly, these analyses provide an overview of the type of evidence used by the FDA to assess the safety and effectiveness of an approved IA-HA product and demonstrate that even similarly designed RCTs of a single product may yield diverse conclusions.

Results from three of the five RCTs are published, including the pivotal trial in 2004; two reported statistical superiority for IA-HA treatment (Table I)[10–12]. In the trial without statistical significance, a prospectively defined subgroup analysis in patients >65 years old with baseline Lequèsne Index (LI) scores >10 statistically favored active treatment. Although the remaining two RCTs have not been published in peer-reviewed literature, complete clinical and statistical reports were submitted to the FDA and are included in the analyses presented here.

Differences between peer review and regulatory review processes are not widely recognized. Clinical trials accepted for FDA review include multiple procedures to ensure scientific integrity of the data and analyses: careful monitoring of investigational sites, adherence to "good clinical practices" (GCP) procedures, quality control and quality assurance standards, and cross-checking of CRF data against primary medical charts. The FDA performs detailed statistical and medical reviews of the data, typically independent, complete re-analyses – none of which are usually available when reports are submitted for peer review. As practicing clinicians must determine their use of approved therapies based on a wide variety of publications and labeling information, a better understanding of the regulatory approval process is relevant. In view of the well-recognized need for OA treatments with minimal systemic toxicities, and the documented safety profile of IA-HA products, the information presented here should help clinicians better evaluate a controversial therapy.

Methods

RCTs INCLUDED IN THE ANALYSIS

Summary data from 18 clinical trials evaluating a single IA-HA product (Supartz®, manufactured by Seikagaku Corporation, Tokyo, Japan, and distributed by Smith & Nephew Orthopaedics, Memphis, TN, USA) were included in a Pre-Marketing Approval application (PMA). Of these, five were double-blind RCTs conducted in compliance with GCP requirements, and considered to meet FDA criteria for review. Individual study reports for each RCT were submitted, including protocol, individually completed CRFs, full data sets, and analyses of safety and efficacy. This entire data set, including original CRFs, was made available to the authors for this integrated analysis. The RCTs were conducted in Germany (1991), Sweden (1993), France (1995), United Kingdom (1996), and Australia (1996); they are summarized in Table I and will be referred to in the manuscript by country of origin. Several of the current authors served as primary investigators in these trials.

TRIAL DESIGN OVERVIEW

All five RCTs were similar in design: prospective, randomized, placebo-controlled, and evaluated a treatment regimen of 5 weekly arthrocenteses and injections of either active HA or "placebo" (phosphate buffered saline). One trial (Germany) used a dilute (0.01%) HA formulation as the control injection instead of saline. Another (France) evaluated a three-injection in addition to a five-injection regimen of IA-HA. All RCTs followed patients for at least 3 months (Table I). Efficacy was assessed at weeks 5 and 13 after the first injection in all and at week 9 in four trials; there were additional evaluations at weeks 17, 20 and/or

Table I
Comparison of patient populations, outcome measures, and evaluation time points utilized in the individual trials and the integrated analysis

Country [Reference]	No. of centers	No. of patients			Outcome measures		Evaluation time points
		Total	HA	Control	Primary	Secondary	
Australia [Day *et al.*[11]]	17	223	108	115	WOMAC pain scale	Lequèsne; global assessment; rescue medication	Weeks 5, 9, 13 and 17
France [unpublished]	54	254	(5) 87 (3) 87	80	LI	VAS pain; global assessment; rescue medication	Weeks 5, 9 and 13
Germany [Puhl *et al.*[10]]	25	208	102	106	LI	VAS pain; global assessment	Weeks 5, 9 and 13
Sweden [Lohmander *et al.*[12]]	8	239	119	120	LI	VAS pain global assessment; rescue medication	Weeks 5, 13 and 20
UK [unpublished]	19	231	116	115	VAS pain	VAS pain; LI global assessment	Weeks 5, 9, 13, 17 and 25
Integrated data set	123	1155	619	536	LI		Weeks 5, 9 and 13