International Journal of Surgery 11 (2013) 209–217

Contents lists available at SciVerse ScienceDirect

International Journal of Surgery

journal homepage: www.theijs.com

Review

Serratiopeptidase: A systematic review of the existing evidence

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ARTICLE INFO

Article history:
Received 20 July 2012
Received in revised form
8 December 2012
Accepted 26 January 2013
Available online 1 February 2013

Keywords:
Serratiopeptidase
Serrapeptase
Serratiopeptidase
Proteolytic enzymes
Pharmacokinetics
Pharmacodynamics
Anti-inflammatory agents
Danzen
Serratiapeptase
Serralysin
Adverse drug reactions

ABSTRACT

Background: Serratiopeptidase is a proteolytic enzyme prescribed in various specialities like surgery, orthopaedics, otorhinolaryngology, gynaecology and dentistry for its anti-inflammatory, anti-edemic and analgesic effects. Some anecdotal reports suggest it to possess anti-atherosclerotic effects also, due to its fibrinolytic and caseinolytic properties. Despite being widely used there are few published studies regarding its efficacy. Thus, evidence regarding its clinical utility is needed.

Objective: To evaluate the existing evidence regarding efficacy and safety of Serratiopeptidase in clinical practice.

Evidence acquisition: A systematic review of all the published articles of Serratiopeptidase using Cochrane Library, PubMed, MEDLINE, Clinical Trials.gov, Google, Dogpile and a manual search of bibliographies was conducted from 1st May 2011 till 15th July 2012. Further emails were sent to all the leading pharmaceuticals who are manufacturing this enzyme preparation for any additional information. All studies related to Serratiopeptidase which included Randomised controlled trials (RCTs), meta-analysis of RCTs, placebo-controlled, single-blind, double-blind, open label, prospective trials as well as preclinical studies were screened and analysed. The scientific credibility of the studies was graded according to the Scottish Intercollegiate Guidelines Network (SIGN) grading checklist. A total of 24 studies on clinical efficacy of Serratiopeptidase met the inclusion criteria.

Evidence synthesis: Serratiopeptidase search on Cochrane library revealed 16 results among which 9 were Cochrane Central Register of Controlled Trials 2011, issue 4 studies and 7 were Cochrane Central Register of Controlled trials 2012, issue 3 studies. Of these 16 results, 11 were RCTs on efficacy of Serratiopeptidase. PubMed search also revealed 74 results which showed 16 Clinical trials, out of which 9 were RCTs related to Serratiopeptidase. Bandolier online edition (retrieved on 1/5/2011) showed a review 'Serratiopeptidase-finding the evidence' which included 9 RCTs. The evidence supporting the use of Serratiopeptidase as anti-inflammatory and analgesic agent is based on clinical studies which are of poor methodology. Only few RCTs, which are usually placebo control, with a small sample size are there. The dose and duration of treatment was not specified in some studies, and the outcome of the study was not clearly defined in a few. Data on the safety and tolerability of Serratiopeptidase is lacking in these studies.

Limitations: A thorough search of literature was done to include all the relevant studies but we may have unknowingly missed a few of those studies which have not been published or registered with any of these search engines. The clinical evidence obtained have been graded according to the "Scottish Intercollegiate Grading Network" checklist by two separate reviewers and then coordinated together to give the final grading. Any disagreement between the two reviewers was resolved by discussion with the third reviewer. This was done to minimise bias but still the risk of bias cannot be completely ruled out.

Conclusion: Serratiopeptidase is being used in many clinical specialities for its anti-inflammatory, anti-edemic and analgesic effects. It is even being promoted as a health supplement to prevent cardiovascular morbidity. The existing scientific evidence for Serratiopeptidase is insufficient to support its use as an analgesic and health supplement. The data on long-term safety of this enzyme is lacking. Evidence based recommendations on the analgesic, anti-atherosclerotic efficacy, safety and tolerability of Serratiopeptidase are needed.

1. Introduction

Serratiopeptidase (Serratia E-15 protease also known as serralysin/serratia-protease/serrapeptase) is a proteolytic enzyme that

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http://dx.doi.org/10.1016/j.ijsu.2013.01.010

has been used for reducing inflammation.[1–7] Enteric coated oral formulation of this enzyme is being used commonly in various specialities like surgery, orthopaedics, otolaryngology, gynaecology and dentistry for its anti-inflammatory and anti-edemic properties. The use of enzymes like trypsin,[8] chymotrypsin,[9] bromelain[10] as anti-inflammatory agents came into practice after it was observed during 1950s in USA that parenteral trypsin could be used to relieve post-surgical inflammation and that due to traumatic injury caused by sports[8] as well as inflammation due to conditions like rheumatoid arthritis, ulcerative colitis, and atypical viral pneumonia.

This observation was soon followed by the use of Serratiopeptidase[2] for its anti-inflammatory effects in Japan for the first time. Later during 1960s these parenteral enzyme formulations were replaced by their enteric coated successors to be used orally. During 1980s and 1990s it was proposed by separate research conducted in Europe and Japan that Serratiopeptidase was the most effective agent in reducing inflammation among all other enzyme preparations.[1,3] Serratiopeptidase hence, has been used for almost 40 years in Japan and Europe for pain and inflammation due to arthritis, trauma, surgery, sinusitis, bronchitis, carpal tunnel syndrome and painful swelling of breasts. Apart from its anti-inflammatory activity, Serratiopeptidase is also said to possess analgesic and anti-atherosclerotic effects. This systematic review is an attempt to critically examine the available evidence which exists as regards the efficacy and safety of Serratiopeptidase.

2. Evidence acquisition

2.1. Search criteria

To identify articles, we systematically searched electronic databases and commercial websites for published and unpublished studies, applied inclusion criteria and performed quality appraisals. The databases searched include the Cochrane Library, PubMed, MEDLINE, the Controlled trials registry Clinical Trials.gov, Google, Dogpile. A manual search from reference lists of relevant articles was conducted and Pharmaceutical companies were contacted through emails for additional information on pharmacokinetics, pharmacodynamics, efficacy and safety of Serratiopeptidase. The following search terms were used either independently of each other or in combinations: Serratiopeptidase, serrapeptase, serratiopeptidase, proteolytic enzymes, pharmacokinetics, pharmacodynamics, anti-inflammatory agents, danzen, serratiapeptase, serralysin, adverse drug reactions.

2.2. Inclusion criteria

Eligible studies were required to report results on Serratiopeptidase efficacy and safety. All articles available on efficacy were included. All articles were required to be complete and available in english. Studies were selected for inclusion in our systematic review if they met the inclusion criteria: double-blind, single-blind, open label, placebo-controlled, randomised controlled trials, meta-analysis of RCTs, prospective trials or preclinical studies.

A total of 24 studies on clinical efficacy of Serratiopeptidase met the inclusion criteria. Among which 18 were clinical trials (including 14 RCTs, 3 prospective trials and in 1 trial study design not stated) and 6 were preclinical animal studies. As Serratiopeptidase has been in clinical use for inflammation and pain for a number of years and is being promoted these days for its anti-atherosclerotic effects also. But data on its analgesic and anti-atherosclerotic efficacy was found to be lacking. The RCTs were only a few in numbers (14 RCTs in total excluding the duplicated studies, 11 RCTs found on Cochrane Library and 9 on PubMed search). They had a limited population, not more than 150 patients per group in any of the studies and were of short duration. Therefore prospective studies as well as preclinical studies were also included to appraise evidence on efficacy of Serratiopeptidase.

2.3. Quality appraisal

Critical appraisal of studies was conducted using PRISMA[11] statement (Fig. 1) while the Scottish Intercollegiate Guidelines Network (SIGN)[12] grading for RCTs was used for original studies by two separate reviewers and then coordinated together to validate the final grading. This was done to facilitate transparent and comprehensive reporting of results. Any disagreement between the two reviewers was resolved by discussion with the third reviewer.

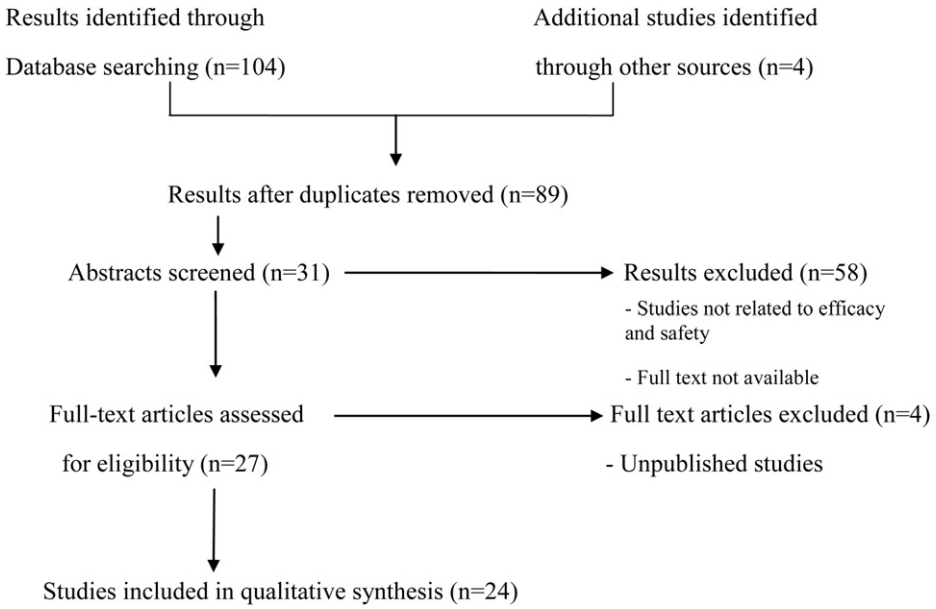

Fig. 1. Preferred reporting items for systematic reviews and meta-analysis (PRISMA)[11] flow diagram of studies included in the review of efficacy of serratiopeptidase.