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Acetylsalicylic acid desensitization in patients with coronary artery disease: A comprehensive overview of currently available protocols

Monica Verdoia [a], Lucia Barbieri [a], Alon Schaffer [a], Matteo Nardin [a], Harry Suryapranata [b], Giuseppe De Luca [a,*]

[a] Division of Cardiology, Azienda Ospedaliera-Universitaria "Maggiore della Carità", Eastern Piedmont University, Novara, Italy
[b] Department of Cardiology, UMC St Radboud, Nijmegen, The Netherlands

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ABSTRACT

Background: Acetylsalicylic acid (ASA) represents the basis of pharmacological therapy for cardiovascular prevention. However, several patients are excluded from the benefits of ASA for hypersensitivity problems, and controversies still exist on their management. The aim of present study was to evaluate the safety and efficacy of ASA desensitization protocols in patients requiring dual antiplatelet therapy for coronary artery disease.
Methods: Literature archives and main scientific sessions' abstracts were scanned for studies describing desensitization protocols for patients with ASA hypersensitivity. Primary endpoint was the tolerance of ASA maintenance therapy (protocol success). Secondary endpoints were: 1) the occurrence of hypersensitivity symptoms during the protocol, 2) the rate of ASA discontinuation at follow-up; 3) recurrent cardiovascular ischemic events.
Results: We finally selected 14 studies out of 335 initially screened citation, reporting complete data on protocol desensitization strategies, with a total of 256 patients. Among them 213 (83.2%) underwent an oral desensitization protocol, while 43 received endovenous ASA. The protocol was successfully completed in 238 out of 256 patients (92.9%), who were subsequently kept on chronic daily therapy with ASA. The weighted success proportion was wP [95%CI] = 93[89.8–96.1]%. Hypersensivity symptoms occurred during the desensitization protocol in 29 patients, with a pooled events rate of 11.3[7.5–15.2]%. All adverse reactions were safely faced with pharmacological interventions. In 11 of these patients, slowing the protocol or restarting another ASA challenge could successfully achieve the tolerance. The rate of ASA discontinuation and major cardiovascular events was extremely low (6.1 and 2.3% respectively).
Conclusions: Aspirin desensitization protocols represent a safe and effective option for the management of patients with a cardiovascular indication to ASA and history of allergy to ASA. Future randomized trials are certainly needed to confirm present findings and provide indications for the optimization of these protocols.

1. Background

Recent advances in percutaneous coronary interventions (PCI) and stent techniques have contributed to enlarge the indication to percutaneous revascularization to a raising number of patients [1–4]. In fact, despite new generations of drug eluting stents have demonstrated faster endothelization, offering the possibility of reducing antiplatelet therapy duration, still acetylsalicylic acid (ASA) represents an essential component of the dual antiplatelet therapy after PCI [5–6].

However, about 1–2% [7] of patients with coronary artery disease is precluded from the cardiovascular benefits of ASA due to a hypersensitivity phenomenon, whose clinical presentation can range from the cutaneous urticaria to respiratory symptoms or systemic anaphylaxis.

The management of these patients, then, is still controvert, especially in the case of a recent PCI with stent implantation, where the use of ibuprofen, increased dose of thienopyridines, or cilostazol have been suggested as an alternative to the traditional dual antiplatelet therapy [8,9].

Recently, the introduction of desensitization protocols has been proposed [10–12], in order to induce tolerance to ASA, with different timing of administration and dosages. Moreover, these protocols have been tested in few patients and none of these protocols has even been validated in randomized trials, therefore rendering still questionable its routine application everyday clinical practice.

In this context, aim of the present meta-analysis was to provide large scale data on the safety and effectiveness of ASA desensitization protocols in patients requiring antiplatelet therapy as secondary prevention for cardiovascular disease.

2. Methods

2.1. Eligibility and search strategy

The literature was scanned by formal searches of electronic databases (MEDLINE, Cochrane and EMBASE) for clinical studies or case series and furthermore the scientific session abstracts, searched on the TCT (www.

* Corresponding author at: Azienda Ospedaliera-Universitaria "Maggiore della Carità", Eastern Piedmont University, Corso Mazzini, 18, 28100 Novara, Italy.
E-mail address: giuseppe.deluca@maggioreosp.novara.it (G. De Luca).

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tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org), AHA (www.aha.org), and ESC (www.escardio.org) websites, for oral presentations and/or expert slide presentations from January 1990 to March 2015. Different combinations of the following key words were used: "acetylsalicylic acid", "ASA", "hypersensitivity", "desensitization"; and "protocol".

No language restrictions were enforced. Inclusion criteria were: 1) patients with documented cardiovascular disease; 2) availability of complete clinical data; and 3) explicit desensitization protocol. Exclusion criteria were: 1) non-cardiovascular indication to ASA, 2) case series on <3 patients; and 3) ongoing studies or irretrievable data.

Hypersensitivity symptoms were defined as cutaneous for urticaria or cutaneous rash, as respiratory for asthma or bronchial spasm and systemic in case of anaphylaxis or oedema of the glottis or angioedema.

2.2. Data extraction and validity assessment

Data were independently abstracted by two investigators (MV, LB). In case of incomplete or unclear data, authors were contacted. Disagreements were resolved by consensus. Data were managed according to the intention-to-treat principle. Outcomes data on the longest follow-up available were collected when available.

2.3. Outcome measures

Primary endpoint was the tolerance of ASA maintenance therapy (protocol success). Secondary endpoints were: 1) the occurrence of hypersensitivity symptoms during the protocol administration, 2) the rate of ASA discontinuation at follow-up; and 3) recurrent cardiovascular ischemic events.

2.4. Data analysis

A systematic review was conducted to calculate the pooled success rate and 95% confidence interval. The pooled median rate of success and adverse events, weighted on the number of patients of each selected trial, were also calculated.

The study was performed in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [13]. The quality of the studies was based on the MINORS criteria for non-randomized trials, assigning a score, expressed on an ordinal scale, allocating 1 point for the presence of each of the following: 1) stated aim of the study; 2) inclusion of consecutive patients; 3) prospective collection of data; 4) endpoint appropriate to the study aim; 5) unbiased evaluation of the endpoints; 6) follow-up period appropriate; and 7) loss to follow up not exceeding 5% of patients [14].

3. Results

A total of 18 studies out of 335 citations reporting data on protocol desensitization strategies were initially identified [7,10–12,15–24]. Fig. 1 displays the flow-chart for the selection of studies. One study was excluded because representing a single case report [25], other two studies [26,27] because proposing alternative antiplatelet strategies and one because presenting cases of desensitization in patients without cardiovascular disease. Therefore, 14 studies were finally selected, with a total of 256 patients included in our analysis. Among them, 213 (in 13 studies) underwent an oral desensitization protocol, while 43 (1 study) [12] received endovenous ASA. Main characteristics of included studies are displayed in Table 1.

Mean protocol duration was 3.4 h, but in one study increasing ASA doses were administered within 6–10 days [23]. In one study, the desensitization protocol was differentiated for patients with previous systemic hypersensivity symptoms who were considered a higher risk population [18].

Scheduled follow-up was planned in 5 studies (in 2 studies only in-hospital, 16,21), whereas in the other 9, the follow-up period was variable and data on the longest follow-up available were reported for each patient. History of hypersensivity manifestations to ASA was reported as cutaneous in 55.8% of patients, 13% of patients reported respiratory symptoms while 37.7% of them a systemic reaction. The indication for ASA was percutaneous coronary interventions in 90.4% of patients. A STEMI was observed in 21.4% of patients. Main demographic features for included patients are listed in Table 2.

3.1. Primary endpoint

The protocol was successfully completed in 238 out of 256 patients, (92.9%) who subsequently received daily chronic therapy with ASA. The weighted success proportion was wP [95%CI] = 93[89.8–96.1]%. The median protocol success rate was 96.7[93.2–98.2]%. Fig. 2 shows the success rate and weights for each study.

3.2. Secondary endpoints

3.2.1. Adverse reactions

An adverse reaction, defined as hypersensivity symptoms occurring during the desensitization protocol, was observed in 29 patients, with a

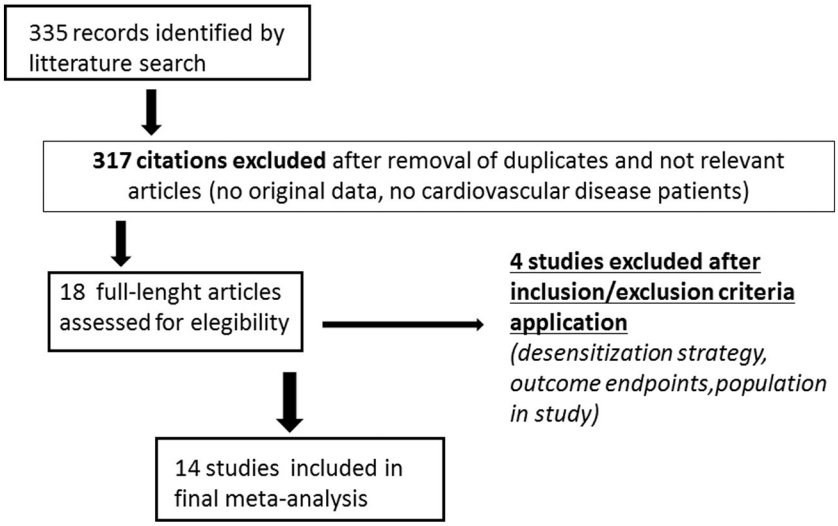

Fig. 1. Flow diagram of the systematic overview process.