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Case Report

Acyclovir desensitization. A case report and a review of desensitization strategies

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Abstract

Introduction: Acyclovir is a synthetic purine nucleoside analog that is used to treat infections caused by herpes simplex virus (HSV) and varicella zoster virus (VZV) by targeting the viral enzyme thymidine kinase. However, its use can lead to hypersensitivity reactions (HR) in rare cases, resulting in treatment discontinuation. Rapid drug desensitization (DD) by intravenous or oral administration protocols are used in these patients in order to avoid treatment discontinuation. This approach has been proven to be effective and safe. Here, we review all the desensitization strategies adopted so far, and also report our experience.

Methodology: We reviewed all reports related to acyclovir desensitization; focusing on skin test results, protocols and premedication performed, and their effectiveness. We also report on the case of a 74-year-old woman affected by multiple myeloma who developed HR to acyclovir. She underwent skin tests, and lymphocyte proliferation test (LPT) with acyclovir, and was subsequently subjected to oral desensitization.

Results. Six articles met the inclusion criteria and were analyzed in this review, along with a case report. All DD procedures were well-tolerated, with only mild reactions reported in one patient. Skin tests gave negative results but one result was deemed doubtful response. Moreover, the LPT performed in our case had positive result, indicating a hypersensitive immune response to acyclovir.

Conclusions. Acyclovir desensitization is a safe and effective approach for patients experiencing HR. Standardized in vivo and in vitro testing are required to better estimate the risk of DD and find the safest individualized DD protocol.

Key words: acyclovir; desensitization; allergy.

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Introduction

Acyclovir is a synthetic purine nucleoside analog that inhibits herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), and varicella zoster virus (VZV). Its inhibitory effect is very specific because it targets the enzyme thymidine kinase (TK) that is expressed by HSV and VZV. This viral enzyme transforms acyclovir to acyclovir monophosphate, which is a nucleotide analog. Cellular guanylate kinase converts monophosphate into diphosphate, which is then turned into triphosphate by a variety of cellular enzymes. Acyclovir triphosphate inhibits herpes virus DNA replication in vitro. This is performed in three steps: i) competitive inhibition of viral DNA polymerase, ii) inclusion into and termination of the developing viral DNA chain, and iii) deactivation of viral DNA polymerase [1].

Acyclovir is an agent used to treat infections caused by the herpes simplex virus (HSV) and it is US Food and Drug Administration (FDA)-approved to treat genital herpes and HSV encephalitis. Non-FDA-approved indications are mucocutaneous HSV, herpes zoster (shingles), and varicella zoster (chickenpox). Prophylactic use of acyclovir should also be considered in patients affected from primary or secondary immunodeficiency [2,3]. It can be administered orally, intravenously, or topically.

However, administration of acyclovir or other structurally close antivirals such as famciclovir, valacyclovir, and penciclovir, is rarely associated with hypersensitivity reactions (HR). Indeed, up to 3% of patients on acyclovir therapy have reported allergies such as hives, itching, and rash [4]. Moreover, data about cross-reactivity among these structurally related

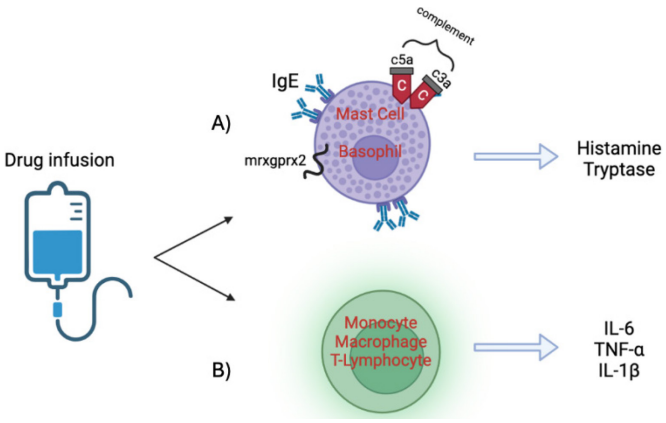
antivirals is not yet well established, but approximately 50% of patients tolerate famciclovir after reaction to valacyclovir or acyclovir [5].

Possible mechanisms of HR may be one these four classic pathways: (1) IgE-mediated reactions, (2) reactions due to cytokine release, (3) mixed mechanisms (1 + 2), and (4) reactions due to complement activation (Figure 1). Skin tests may suggest the presence of a possible drug-specific IgE (type I mechanism of Gell and Coombs classification) and stratify the risk of HR.

A drug desensitization (DD) approach is implemented in patients who experience HR, and other therapeutic options are either not available or less effective, and proven to be effective in restarting acyclovir or avoiding its discontinuation [6,10]. DD procedures involve induction of a temporary tolerance to the medication responsible for HR and is performed by administering the offending drug with increasing dosages over a longer period compared with standard infusion schedule, until the full therapeutic dose is administrated and tolerated. Generally, classic intravenous DD protocols last about 6 hours and include 12 consecutive steps using three bags of solutions with increasing drug concentrations. Each step takes 15 min with a 2 to 2.5-fold increase in the rate of drug administration, excluding the last step (step 12), which lasts around 3 hours [11]. DD for a specific medication can be performed in patients who develop an immediate hypersensitivity type I reaction and other therapeutic options are not available, or when other drugs may be less effective. Nevertheless, DD is not recommended in patients who experienced life-threatening immunocytotoxic reactions, vasculitis, or severe cutaneous reactions because of the potential life-threatening nature of these events. The hypothesis regarding the mechanism of DD is that increasing sub-therapeutics dosages of the antigens (medication) bind to IgE anchored to the surface FcεRI receptors, but the cross-linking does not occur, or the antigen may induce a rapid internalization of specific IgE-cross-linked receptors depleting these receptors with subsequent mast cell and basophil unresponsiveness [12]. Few data are available about the safety and efficacy of acyclovir desensitization.

The aim of this article is to review the DD strategies for acyclovir, by highlighting efficacy, limitations, and future perspectives; and describe our experience with a case report.

Figure 1. Mechanism of hypersensitivity reactions.



A. IgE-mediated reaction consists of a specific anti-drug IgE that crosslinks on mast cell and basophil's membrane when the drug is administered. Moreover, medications can induce activation of the same cells through the MRXGPRX2 receptor. On the other hand, drugs can trigger the complement cascade leading to the release of c3a and c5a anaphylatoxins resulting in the activation of mast cells and basophils with consequent histamine, tryptase and platelet activating factor (PAF) release. Usually, the signs and symptoms are urticaria, pruritus, flushing, shortness of breath, dyspnea, throat tightness, abdominal pain, hypotension, and cardiovascular collapse (anaphylactic shock). **B.** Monocytes, macrophages, and T cell may be responsible for hypersensitivity reactions. IL-6, TNF-α, and IL-β may cause chills, fever, hypotension, nausea, vomiting, fatigue, dyspnea, and oxygen desaturation (infusion related reaction or cytokine release reaction).

Methodology

Literature review

Search strategy

This study was performed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. We searched MEDLINE, LILACS, and the ISI Web of Science databases (inception to 31 January 2024) for original articles, clinical trials, case reports, abstracts from congresses, and editorial letters assessing the effectiveness of DD procedures in patients who developed HR to acyclovir. We used the following search terms: desensitization, rapid desensitization, acyclovir, and aciclovir. Electronic search was integrated with a manual search of the reference lists. Studies were included if they involved patients who developed HR and underwent desensitization procedures during acyclovir administration. Studies were excluded if they did not report on the outcome of interest. Moreover, the Rayyan automation tool was used to detect ineligible articles or duplicates [13].

Data quality assessment and management

All articles were screened using the title and abstract. Relevant articles were selected for this review. Data on the first author, publication year, gender, age, disease, grade of HR during the last infusion (according to World Allergy Organization anaphylaxis guidance,

2020) [14], skin tests results, drug desensitization protocol (number of days, number of bags, number of steps) and premedication adopted, and breakthrough reaction during the first desensitization protocol were extracted. Furthermore, we assessed the quality of each study through the Joanna Briggs Institute critical appraisal tool for case reports to assess the possibility of bias in the studies' design [15]. This tool consists in 8 questions that assess whether the studies clearly describe the patients' demographic information, patients' history, patients' current clinical condition, diagnostic test, intervention/ treatment, post-intervention clinical condition, adverse events, and takeaway lesson. For each question, the assessor provides an answer, which can be yes, no, or unclear. The result of the overall appraisal is up to the assessor who may consider a study as included, excluded, or seek further information.

Case report

Patient characteristics

A 74-year-old woman was affected by multiple myeloma and chronic renal insufficiency, and developed HR after several months of acyclovir intake. At that time, she was taking only acyclovir as prophylaxis under multiple myeloma treatment. However, urticarial rash of the limbs developed and acyclovir was suspended. Chemotherapy for multiple myeloma was continued without occurrence of urticaria. She was examined and desensitized in December 2023 at the Internal Medicine Unit of University Hospital of Bari (Italy).

Acyclovir

Acyclovir (Zovirax®) 400 mg/5 mL oral suspension and acyclovir (Zovirax®) 200 mg tablet (manufactured by GlaxoSmithKline, Research Triangle Park, NC 27709, USA), were used for the oral DD schedule. On the other hand, acyclovir (Zovirax®) 250 mg powder was used for preparation of a solution for infusion which was used for performing skin tests.

Skin tests

Patient was subjected to skin prick test (SPT) and intradermal test (IDT) with acyclovir. The drug was used diluted with 5 mL of saline (50 mg/ml) for SPT, while acyclovir was diluted 100-fold (0.5 mg/mL) and 10-fold (5 mg/mL) with saline, respectively, for IDT, and compared to the solution used for SPT. Histamine (10 mg/mL for SPT and 0.002 mg/mL for IDT) and saline were used as the positive and negative control, respectively.

Lymphocyte proliferation test

The case was investigated using the flowcytometry-based proliferation assay. The patient's peripheral blood mononuclear cells (PBMC) were isolated, stained with carboxyfluorescein succinimidyl ester (CFSE), and cultured for 5 days with acyclovir (using three different concentrations: 30, 3 and 0.3 μg/mL), phytohemagglutinin (PHA; as positive control), or left untreated (negative control). PBMCs were then harvested and stained with anti-CD3 and -CD19 antibodies to distinguish T and B cells before flowcytometry analysis. We calculated the stimulation index by normalizing the percentage of proliferating T or B cells in stimulated cultures on the percentage of proliferating T or B cells in untreated cultures; a ratio ≥ 2 was considered positive.

Drug desensitization schedule

Acyclovir desensitization was performed by preparing three different solutions for oral administration: dilution B was prepared using 5 mL of acyclovir oral suspension diluted in 5 mL of water (40 mg/mL); dilution A was prepared diluting 1 mL of dilution B in 9 mL of water (4 mg/mL); solution C was the entire acyclovir 200 mg tablet. The DD protocol consisted of 9 consecutive steps with increasing doses at each dilution. Each step lasted 15 min. Altogether, the drug administration schedule lasted almost 135 minutes. DD protocol for acyclovir is shown in Table 1.

Table 1. Acyclovir oral desensitization schedule. Target dose: 400 mg.

Step	Dilution	Dose administered	Time	mg administered
1	A	0.25 mL	15	1
2	A	0.5 mL	15	2
3	A	1 mL	15	4
4	A	2 mL	15	8
5	B	0.3 mL	15	12
6	B	0.6 mL	15	24
7	B	1.25 mL	15	50
8	B	2.5 mL	15	100
9	C	1 tablet	15	200
Total			135	401

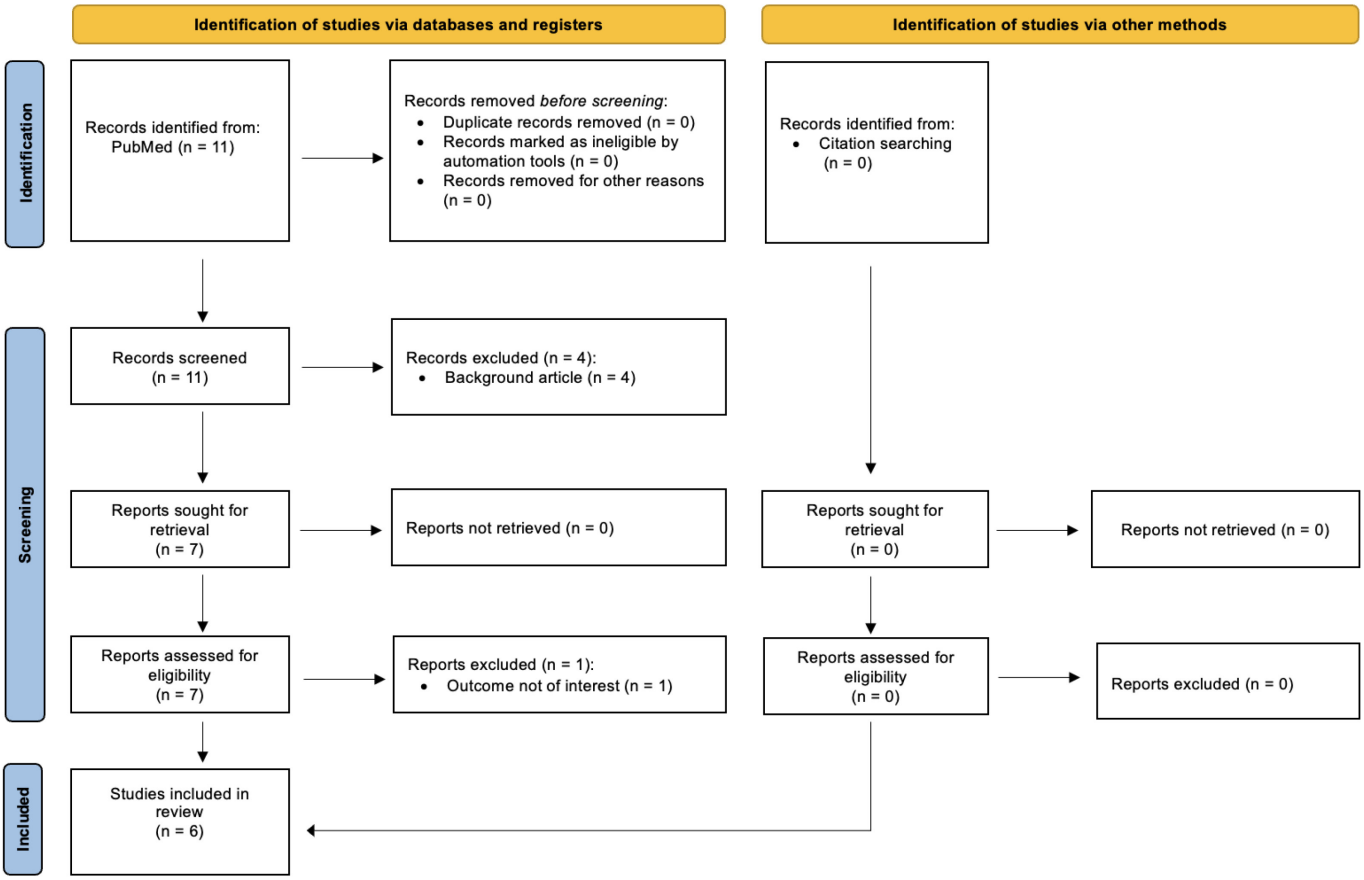
Dilution A: 1 mL of dilution B + 9 mL of water [4 mg/mL]; dilution B: acyclovir oral liquid solution 400 mg/5 mL + 5 mL of water [40 mg/mL]; dilution C: acyclovir 200 mg tablet.

Table 2. Patients' characteristics and acyclovir desensitization protocols.

Author, year	Patient (gender, age)	Ongoing disease	Route of acyclovir administration	HR reaction	Grade of HR	Skin test results	DD schedule (route, protocol, premedication)	Breakthrough reaction during DD
Henry *et al.* [6]	F, 65	HSV infection	Orally	Face and extremities swelling, nausea, vomiting, diarrhea, ocular pruritus and chills	3	Doubtful	Orally; 1 day; 14 steps; nr	Mild nasal flushing
Kawsar *et al.* [7]	F, 48	HSV type 2 infection	Orally	Maculopapular rash	1	Not performed	Orally; 5 days; 11 steps; x	None
Snape *et al.* [8]	F, 29	HSV/VZV infection with acute retinal necrosis	Intravenously	Macular rash, facial angioedema, and chest tightness	3	Not performed	Orally; 1 day; 15 steps; y	None
Jain *et al.* [9]	F, 8	HSV with encephalitis	Intravenously	Limb swelling, diffuse erythema	1	Negative	Intravenously; *; nr	None
Andrade *et al.* [4]	F, 69	Prophylaxis for myelodysplastic syndrome / myeloproliferative disorder	Orally	Throat and lip swelling, face erythema	2	Not performed	Orally; 1 day; 15 steps; x, y, z	None
Gülen *et al.* [10]	M, 59	HSV with encephalitis	Intravenously	Lip and tongue angioedema, maculopapular rash	1	Not performed	Intravenously; 1 day; 6 steps; x, y	None
Case report (present study)	F, 74	Prophylaxis for multiple myeloma	Orally	Urticarial rash of the limbs	1	Negative	Orally; 1 day; 9 steps; none	None

DD: drug desensitization; F: female; HR: hypersensitivity reaction; HSV: herpes simplex virus; M: male; nr: not reported; VZV: varicella zoster virus; x: antihistamines; y: corticosteroids; z: antileukotrienes. * Protocol started with the target dose diluted 10^6-fold, and the dose was progressively doubled every 30 min till full concentration was achieved.

Figure 2. Flow diagram of research screening.



Search strategy: #1 Desensitization OR rapid desensitization; #2 Acyclovir [Ti;Ab] OR aciclovir [Ti;Ab]; #1 AND #2

The target dose was 400 mg according to the clinicians' schedule therapy planned for the patient (acyclovir 400 mg twice a day).

Results

Study selection and quality assessment

A total of 11 articles were identified by our search strategy and underwent the screening phase: 4 of them were excluded as they were not pertinent to the topic. Of the remaining 7 eligible articles, 1 was excluded as it did not report the outcome of interest. Thus, we included 6 articles in this review (Figure 2); all with sufficient quality to be assessed and analyzed according to the critical appraisal tool adopted (Supplementary Table 1).

Characteristics of the studies

The 6 studies included 6 patients (5 adults and 1 child), of which 4 were affected with HSV infection, and 1 with myelodysplastic syndrome/myeloproliferative disorder. Moreover, we included our patient affected with multiple myeloma in our analysis (Table 2). The mean age was 50.3 years. Acyclovir was administered orally in 4 patients and intravenously in 3 patients. Grade of HR ranged from 1 to 3 (mean, 1.7).

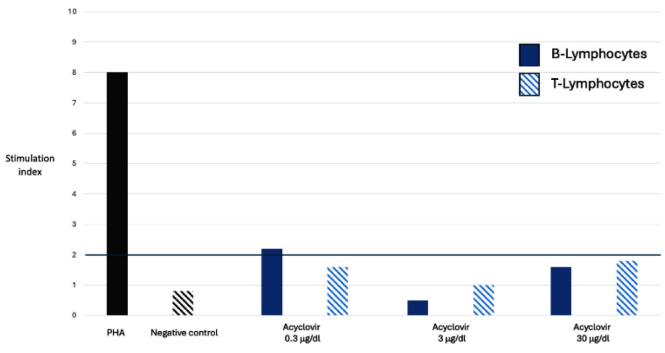
Skin test results

Skin tests were performed only in 2 cases out of 7. The skin test results were deemed doubtful in 1 reported case; while in our case, the skin tests produced negative result.

Lymphocyte proliferation test

The lymphocyte proliferation test provided a positive ratio for B cells (stimulation index = 2.2) with the lowest dose of acyclovir and was thereby considered positive. T cells, however, did not proliferate in response to acyclovir stimulation. Thus, an immediate hypersensitivity reaction may be considered (Figure 3).

Figure 3. Flow cytometry-based proliferation test.



PHA: phytohemagglutinin. The bold horizontal line demarcates the limit for the test to be considered positive: stimulation index ≥ 2.

Results of acyclovir desensitization

All DD schedules were performed and concluded in a single day, except for one protocol which lasted 5 days; with a minimum of 6 steps and a maximum of 15 steps. Premedication was used in 4 out of 7 patients. All patients tolerated the DD except for 1 patient who complained of mild nasal flushing. However, this mild reaction did not lead to acyclovir discontinuation.

Discussion

Acyclovir represents the best therapeutic option in patients infected with HSV/VZV and in immunosuppressed patients who need antiviral prophylaxis. Unfortunately, mild-to-severe HR can occur during this treatment. Thus, an allergy work-up and DD procedure should be taken into consideration to increase the likelihood of acyclovir continuation.

Evidence on DD were obtained from chemotherapy, monoclonal antibody, and recombinant enzymes studies, showing efficacy in almost all cases [11,16–18]. There are only a few published reports on DD of acyclovir, but there is evidence that the DD approach is effective.

To the best of our knowledge, this is the first review on acyclovir desensitization. We found that the desensitization procedure was tolerated in 100% of patients from the outset and no HR occurred during the subsequent courses. Only 1 patient developed mild nasal flushing but there was no interruption of the therapy. Both oral and intravenous routes of administration proved safe and effective.

On the other hand, we noted that no patient had positive skin test to acyclovir, except 1 with doubtful result. This suggests that mechanisms other than specific IgE-mediated mechanism might be involved, such as direct basophils/mast cells by the drug, involvement of MRXGPRX2 receptor, or complement activation with anaphylatoxins (C3a, C5a) production and subsequent mast cell/basophil activation. In these cases, skin tests can be negative, as shown for taxane hypersensitivity where immediate HRs are usually not IgE-mediated and skin tests are negative. However, rapid desensitization for taxane is effective and safe, similar to desensitization for acyclovir [19].

Skin tests for acyclovir are not standardized nor validated. Thus, the sensitivity of the skin test could be low and false negatives may occur. For this reason,

standardized in vitro testing, such as assay for acyclovir IgE, basophil activation test (BAT), or lymphocyte proliferation test would be helpful. Indeed, we subjected our patient to the lymphocyte proliferation test with acyclovir in order to assess the reactivity of the immune system to the drug. The assay produced positive results for B lymphocytes, indicating a hypersensitive and immediate immune response to acyclovir. To our knowledge, this is the first case in which a patient who experienced an allergic reaction to acyclovir has undergone this test.

Finally, based on the findings of this review and our case report, we can conclude that oral and intravenous desensitization to acyclovir can be a safe and effective approach, both in patients affected by HSV/VZV infection and hematological diseases.

Conclusions

DD represents a safe and effective choice for restarting acyclovir in patients who experienced HR. Different approaches could be valid, but more studies on the stratification of HR risk during this procedure are needed to find the safest and fastest DD protocol. Moreover, skin tests are still challenging, and in vivo and in vitro testing should be upgraded and implemented to better stratify the risk of HR.

Authors' contributions

FS: conceptualization, writing — original draft preparation, methodology; RR: data curation, supervision; NC: writing — reviewing and editing, investigation, methodology; AV: supervision, validation; AGS: data curation, supervision, validation; ADG: writing — reviewing and editing, conceptualization, validation. All authors approved the final manuscript.

Ethics statement

Written informed consent was obtained from the participant/patient for the publication of this case report.

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Data availability statement

Data and materials used in this case report are based on the medical records, imaging studies and pathological findings of our patient. Due to privacy and confidentiality considerations, access to the specific patient data and materials is restricted. However, anonymized and de-identified data may be made available for research purposes upon reasonable request, in compliance with institutional policies and ethical guidelines.

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Conflict of interests

No conflict of interests is declared.

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Annex – Supplementary Items

Supplementary Table 1. The Joanna Briggs Institute Critical Appraisal Tool — checklist for case reports.

Study	1	2	3	4	5	6	7	8	Overall appraisal
Henry *et al.* [6]	Y	Y	Y	Y	U	Y	Y	Y	Include
Kawsar *et al.* [7]	Y	Y	Y	Y	Y	Y	Y	Y	Include
Snape *et al.* [8]	Y	Y	Y	Y	Y	Y	Y	Y	Include
Jain *et al.* [9]	Y	Y	Y	N	U	Y	Y	Y	Include
Andrade *et al.* [4]	Y	Y	Y	Y	Y	Y	Y	Y	Include
Gülen *et al.* [10]	Y	Y	Y	Y	Y	Y	Y	Y	Include

Y: yes; N: no; U: unclear; NA: not applicable. Overall appraisal: include; exclude; seek further information.