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ORIGINAL RESEARCH ARTICLE

# Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A National Analysis of Data from 10-Year Post-marketing Surveillance

**Francesca Renda[1] · Giovanni Landoni[2,3] · Renato Bertini Malgarini[1] · Alessandro Assisi[1] · Maria Luisa Azzolini[2] · Marta Mucchetti[2] · Giuseppe Pimpinella[1] · Luca Pani[1]**

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**Abstract**

*Introduction* Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, severe and potentially fatal cutaneous adverse drug reaction (the mortality rate is up to 10 %) associated with numerous and apparently heterogeneous drugs. The aetiology is unknown.

*Objective* To report Italian cases of DRESS over a 10-year period.

*Methods* We searched the National Pharmacovigilance Network (NPN) for the term 'drug reaction with eosinophilia and systemic symptoms' from 1 January 2004 to 1 January 2014, to identify all reports of DRESS. Each case was checked to avoid duplication.

*Results* In the NPN, we identified 91 serious cases of DRESS: 68 were spontaneous, still-unpublished reports, while 23 additional cases were derived from screening of the scientific literature, performed by marketing authorization holders. Notably, the single common element linking all cases of DRESS was intake of a drug containing an aromatic ring.

*Conclusion* Thanks to the largest national DRESS case series ever reported, we were able to hypothesize, for the first time, that there is an association between use of drugs containing an aromatic ring in their chemical structure and DRESS. This might aid understanding of the aetiology of DRESS and facilitate diagnosis.

**Key Points**

Drug reaction with eosinophilia and systemic symptoms (DRESS) is increasingly reported in spontaneous pharmacovigilance databases and in the literature.

We report the largest national case series ever published (91 patients), characterized by a low mortality rate (1.1 %), even though use of the suspected drug was promptly interrupted in only 27 % of cases.

We noted that the chemical structure of all drugs included in this case series incorporated an aromatic ring.

## 1 Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, severe cutaneous adverse drug reaction (ADR) with skin eruption and multi-organ impairment [1]. The actual definition of DRESS was proposed by Bocquet et al. in 1996 [2] and updated in 2007 by the Register of Severe Cutaneous Adverse Reactions (RegiSCAR) Study Group [3].

DRESS is associated with a limited number of drugs, when compared with other ADRs. The most commonly

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✉ Giovanni Landoni
landoni.giovanni@hsr.it

[1] Italian Medicines Agency, Rome, Italy

[2] IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

[3] Vita-Salute San Raffaele University, Milan, Italy

reported agents are aromatic antiepileptic drugs (carbamazepine, phenytoin, phenobarbital and lamotrigine) [4], allopurinol and antibiotics (sulfasalazine, vancomycin and minocycline) [5, 6]. The pathogenesis is unclear, but a series of genetic polymorphisms (epoxide hydroxylase [2], slow *N*-acetylator phenotype [7] and human leukocyte antigen [8]) and reactivation of members of the Herpesviridae family (Epstein-Barr virus, cytomegalovirus, varicella zoster virus, human herpes virus 6 and 7) [9, 10] seem to be involved. The actual incidence of DRESS syndrome is yet to be determined. A recent retrospective study reported a prevalence of 2.5/10,000 hospitalized patients [11].

Clinically, DRESS is characterized by dermatological and systemic manifestations, which usually develop 10–30 days after drug administration [12]. All patients have cutaneous manifestations, such as a morbilliform rash starting from the upper part of the body and often associated with oedema. Other cutaneous lesions and mucosal involvement are also described [5, 13]. Fever is present in 90 % of patients and hypereosinophilia in 95 %. Other haematological manifestations are lymphadenopathy (54 %) and atypical lymphocytes (67 %). Internal organ involvement is reported in 91 % of cases, mainly due to hepatic injury (elevation of liver function tests or hepatomegaly). The kidneys and lungs may also be involved [5].

DRESS is a potentially life-threatening condition with mortality of up to 10 % [6], although the RegiSCAR study suggested a mortality of 1.7 % [5]. One out of four patients has at least one recurrence [14], and 11.5 % show long-term sequelae. Elderly patients with DRESS are vulnerable to end-stage organ failure, while young patients subsequently tend to develop autoimmune diseases [15]. There is no reliable standard for the diagnosis of DRESS syndrome, which is still a diagnosis of exclusion. Physicians must exclude other potentially serious conditions, including infections, neoplastic processes, autoimmune disorders, connective tissue diseases and other severe cutaneous drug reactions [6]. The diagnostic criteria set out by the RegiSCAR Study Group [3] are available in the Electronic Supplementary Material as Online Resource 1. Clinical tests to determine the causative medication, such as skin patch tests and lymphocyte transformation tests, have a high positive predictive value but a low negative predictive value. Their use is generally limited and unreliable [16]. Withdrawal of the causative drug and commencement of systemic corticosteroids are the mainstay of treatment in DRESS management. The most severe cases, characterized by organ failure or exfoliative dermatitis, benefit from intensive care or burn unit care [16]. The aetiology is unknown. The case series reported in the literature are, on average, small [5, 12, 14, 15, 17–20].

The National Pharmacovigilance Network (NPN) of the Italian Medicines Agency is a national database collecting information on all ADRs regarding any medicinal product in Italy. Both healthcare professionals and citizens can report ADRs, using a reporting form provided by the Italian Medicines Agency. Marketing authorization holders (MAHs) have to report cases of ADR derived from literature screening. A trained pharmacovigilance professional validates and inserts each report into the NPN. We extracted from the NPN all DRESS cases reported in Italy over a 10-year period, and we identified, for the first time, a common chemical structure in the suspected drugs.

## 2 Methods

We searched the NPN of the Italian Medicines Agency for the term ‘drug reaction with eosinophilia and systemic symptoms’ from 1 January 2004 to 1 January 2014 to identify all reports of DRESS. This entry is the Preferred Term (PT) that identifies the medical concept of DRESS according to the Medical Dictionary for Regulatory Activities (MedDRA), and it contains all synonyms, lexical variants and sub-elements. The primary System Organ Class for this PT is Skin and Subcutaneous Tissue Disorders. The reporting form (see Online Resource 2) ensures the quality of the data included in the national database.

The data that were retrieved included reports of serious ADRs sent by different categories of reporters (healthcare professionals, patients and MAHs) to the NPN. Data were extracted by two expert operators (FR and MM), and disagreement was solved by consensus. All cases were checked for possible duplication before being included in the analyses. If similarity in the patient’s age, sex, date of reaction, duration of reaction and suspected causative drug existed, the whole records were examined carefully.

We extracted from the NPN the following data: the patient’s age, sex, timing of occurrence of the ADR, clinical outcome, suspected drug(s) involved, length of treatment, condition leading to administration of the suspected drug(s), interruption of the suspected drug(s) and seriousness of the ADR (classified by the reporter as serious or non-serious). An ADR was classified as serious if it fulfilled at least one of the following criteria: resulted in death; required hospitalization or prolongation of a pre-existing hospitalization; resulted in persistent or significant disability/incapacity; or was life-threatening or led to a congenital anomaly/birth defect or another medically important condition. Reports with incomplete data were not deleted, and we performed no data imputation. The chemical structures of the suspected drugs were extracted from PubChem Substance.

The Regional Centres for Pharmacovigilance performed the causality assessment, using the Naranjo algorithm for standardized case causality assessment [21], whenever a report was included in the NPN. Causality assessment allowed evaluation and classification of the causal relationship between drug intake and the onset of an ADR as definite, possible, probable or doubtful.

The proportional reporting ratio (PRR) was calculated for each drug associated with at least three reports of DRESS. The PRR summarizes the strength of the association between an ADR and a drug. It compares the frequency of a particular ADR (in this case, DRESS) in individuals taking a specific drug with the frequency with which the same adverse event occurs in patients taking other drugs, i.e. all drugs present in the database. A PRR >1 suggests that the adverse event is more commonly observed in individuals taking the drug of interest than in patients taking the comparison drugs.

The Micromedex® drug-interaction database was checked when any combination of suspected and/or concomitant drugs was reported, in order to identify any potential drug–drug interaction that could have caused the ADR.

The relationship between the number of cases and years was estimated using linear regression in Stata 13 software.

To identify case series of DRESS from the literature, BioMed Central, PubMed, Scopus and Embase were searched for pertinent studies with no time limits and no language restrictions (updated on 1 January 2014) by three different investigators using the entry text 'DRESS [Title/Abstract]' for BioMed Central and PubMed, 'ABS (dress) OR TITLE (dress))' for Scopus and 'dress:ab,ti' for Embase. The references of retrieved articles were checked carefully.

## 3 Results

Over a 10-year period, from January 2004 to January 2014, 172,596 ADRs were reported and recorded in the NPN; of these, 11,702 were classified as serious cutaneous ADRs. Among the serious cutaneous ADRs, we identified 91 cases of DRESS, with a significant increase in reporting during the study period ($p = 0.01$; $R^2 = 0.64$) [see Online Resource 3].

Sixty-seven cases were unpublished, spontaneous reports, while 23 additional cases were included in the database from screening of the scientific literature performed by MAHs. Fifteen of these 23 reports were published in Medline-indexed journals, while the others came from minor journals or were published as abstracts/posters at national congresses (a full list of these 23 reports is available as Online Resource 4). The extracted data are fully available online (see Online Resource 5).

### 3.1 Characteristics of Adverse Drug Reactions

Fifty-eight patients (64 %) in the present case series were female. The median age was 59 years (interquartile range 33–71), ranging from 2 to 96 years. Autoimmune diseases were already present in only four of the 91 cases (4.4 %). The clinical conditions leading to drug administration were mainly nervous disorders (e.g. epilepsy), infections and hyperuricaemia (see Table 1).

Although 79 cases led to hospitalization or life-threatening situations, the outcome was favourable in the vast majority of cases. Only one patient (1.1 %) died, while three developed permanent sequelae.

At the time of the data extrapolation, the Naranjo score [21] was calculated for 39 of the 68 unpublished cases, with 23 judged as probable and 16 as possible.

Nine cases occurred during the first week of treatment with the suspected drug (from day 0 to day 7), 11 cases occurred during the second week of therapy (days 7–14), 27 between days 15 and 30, 17 cases after a treatment period of 30–60 days and three after 60 days of therapy. For the remaining 23 cases (from the literature), it was not possible to establish the timing of the onset of the ADR. No difference in the suspected drugs was seen between early and late reactions.

In 24 of the 91 cases, the suspected drug(s) were discontinued at the time of diagnosis; in two cases, the suspected drug(s) had been discontinued before diagnosis and in the remaining 64 cases, the suspected drug(s) were discontinued between 1 day and 2 months after diagnosis.

### 3.2 Characteristics of Suspected Drugs

The drugs most frequently associated with DRESS were allopurinol, carbamazepine, phenobarbital, sulfasalazine, lamotrigine, vancomycin, amoxicillin, acetaminophen and strontium ranelate. The full list is presented in Table 1. Their chemical structures and their corresponding PRRs are shown in Online Resource 6.

The most commonly involved drugs corresponded to medications used for nervous system disorders and bacterial infections. Treatment with multiple medications (suspect and concomitant) was described in 66 cases, and in 23 of these cases (25 % of the total), the patient was using more than one drug identified as suspect by the reporter and associated with DRESS. The analysis of known drug interactions did not identify any association that increased the risk of DRESS occurrence (Table 2).

**Table 1** Causative drugs associated with drug reaction with eosinophilia and systemic symptoms (DRESS) and the indications that led to their administration

| Drug (no. of cases) | Therapeutic indications | No. of cases ($N = 125$) | Percentage |
|---|---|---|---|
| Carbamazepine (10) | Neurological and neurosurgical disease | 29 | 23.2 |
| Phenobarbital (8) | | | |
| Phenytoin (5) | | | |
| Lamotrigine (3) | | | |
| Levetiracetam (1) | | | |
| Mitoxantrone (1) | | | |
| Oxcarbazepine (1) | | | |
| Amoxicillin–clavulanate (4) | Infectious disease or prophylaxis | 26 | 20.8 |
| Ceftriaxone (4) | | | |
| Vancomycin (4) | | | |
| Teicoplanin (2) | | | |
| Trimethoprim + sulfamethoxazole (2) | | | |
| Amoxicillin (1) | | | |
| Cefixime (1) | | | |
| Clarithromycin (1) | | | |
| Cubicin (1) | | | |
| Gentamicin (1) | | | |
| Levofloxacin (1) | | | |
| Minocycline (1) | | | |
| Rifampicin (1) | | | |
| Rifaximin (1) | | | |
| Teicoplanin (1) | | | |
| Allopurinol (20) | Hyperuricaemia | 20 | 16 |
| Sulfasalazine (8) | Autoimmune or inflammatory disease | 15 | 12 |
| Acetaminophen (3) | | | |
| Hydroxychloroquine sulfate (2) | | | |
| Diclofenac (1) | | | |
| Leflunomide (1) | | | |
| Lamotrigine (4) | Psychiatric disorder | 13 | 10.4 |
| Carbamazepine (1) | | | |
| Escitalopram (1) | | | |
| Haloperidol (1) | | | |
| Lithium carbonate (1) | | | |
| Olanzapine (1) | | | |
| Paroxetine (1) | | | |
| Quetiapine (1) | | | |
| Sertraline (1) | | | |
| Valproate (1) | | | |
| Ramipril (2) | Cardiovascular disease | 9 | 7.2 |
| Ticlopidine (2) | | | |
| Acetylsalicylic acid (1) | | | |
| Atenolol (1) | | | |
| Enoxaparin (1) | | | |
| Furosemide (1) | | | |
| Ramipril + hydrochlorothiazide (1) | | | |

**Table 1** continued

| Drug (no. of cases) | Therapeutic indications | No. of cases ($N = 125$) | Percentage |
|---|---|---|---|
| Esomeprazole (2) | Gastroenteric disease | 7 | 5.6 |
| Lansoprazole (1) | | | |
| Pantoprazole (1) | | | |
| Pegylated interferon alfa-2A (1) | | | |
| Ribavirin (1) | | | |
| Telaprevir (1) | | | |
| Strontium ranelate (3) | Osteoporosis | 4 | 3.2 |
| Alendronic acid + colecalciferol (1) | | | |
| Capecitabine (1) | Neoplastic disease | 3 | 2.4 |
| Cladribine (1) | | | |
| Chlorambucil (1) | | | |

The sum exceeds the total number of 91 reported cases, because in 23 reports, more than one drug was suspected to be the causative agent associated with DRESS

Notably, all drugs included in this case series incorporated an aromatic ring in their chemical structure. This was the only common characteristic among all reported cases.

### 3.3 Literature Review

Our systematic search of the international literature identified seven case series that included more than 25 patients (see Online Resource 7). All suspected drugs reported in these case series have an aromatic ring in their chemical structure. Notably, only two of these case series were larger than the present one [5, 22], and both of them included more than one country.

## 4 Discussion

The most important finding in this study is the hypothesis, proposed for the first time, of a relation between DRESS and use of aromatic ring-containing drugs, which was the only common finding in all 91 patients included in this case series. An aromatic ring was previously recognized as the possible cause of DRESS occurring with antiepileptic drugs [4], but our case series suggests that several other drugs that contain an aromatic ring in their chemical structure may cause DRESS. After analysing all of the international literature published on DRESS, we confirmed that all cases reported so far have been attributed to aromatic ring-containing drugs. At the same time, not all drugs with an aromatic ring have been associated with DRESS, suggesting that the aromatic ring is just one of the factors associated with this syndrome.

Notably, this is the largest national case series ever published. Our literature search identified only two reports that included more than 91 patients (or more than 68 patients, if we consider only the unpublished cases in our case series), and they were both international case series: the international RegiSCAR study, a prospective observational study, which involved eight nations over a 7-year period (2003–2009) and identified 117 patients with DRESS [5]; and a study conducted in 145 patients in Japan and Taiwan in the period 1998–2013 [22].

In our case series, we noted an increase in the reporting of DRESS over time (see Online Resource 3). Even if this increase is not as important as that reported in the international literature, it is likely due to the growing interest in and knowledge about DRESS, following the RegiSCAR publication [5].

The drugs most frequently reported were allopurinol and carbamazepine. Both are widely known to be associated with DRESS. Since NPN is based on spontaneous notifications, published drugs are more likely to be recognized as the causative drug. In addition, drug notoriety strongly influences the Naranjo causality score.

In our case series, we observed a delay between diagnosis and drug interruption in most patients. This could have been due to use of multiple ongoing therapies (making it difficult to identify the responsible drug) and to the severity of the treated disease (malignant tumours, cerebral surgery or post-traumatic epilepsy, making it preferable to continue the treatment even after diagnosis of DRESS). The latency period between the first drug intake and the initial manifestation of DRESS probably made the clinical picture difficult to manage.

**Table 2** Interactions between any combination of suspected and/or concomitant drugs that were co-administered in patients developing a drug reaction with eosinophilia and systemic symptoms (DRESS), identified according to the Micromedex® drug-interaction database

| Interacting active substances | Seriousness | Consequences |
|---|---|---|
| Valproic acid–olanzapine | Moderate | Decreased plasma olanzapine concentrations |
| Escitalopram–lamotrigine | Moderate | Increased risk of myoclonus |
| Phenytoin–furosemide | Minor | Decreased furosemide efficacy |
| Phenobarbital–phenytoin | Minor | Increased or decreased phenytoin concentrations |
| Gentamycin–vancomycin | Major | Nephrotoxicity |
| Atenolol–salicylic acid | Moderate | Decreased antihypertensive effect |
| Ramipril–salicylic acid | Moderate | Decreased antihypertensive efficacy |
| Olanzapine–valproic acid | Moderate | Decreased plasma olanzapine concentrations |
| Lithium–olanzapine | Major | Weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy and brain damage |
| Quetiapine–olanzapine | Major | Increased risk of QT-interval prolongation |
| Phenobarbital–valproic acid | Moderate | Phenobarbital toxicity or decreased valproic acid effectiveness |
| Metronidazole–phenytoin | Moderate | Increased risk of phenytoin toxicity or decreased plasma metronidazole concentrations |
| Amiodarone–phenytoin | Moderate | Increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor) and/or decreased amiodarone concentrations |
| Omeprazole–phenytoin | Moderate | Increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor) |
| Insulin human–levofloxacin | Major | Changes in blood glucose levels and increased risk of hypoglycaemia or hyperglycaemia |
| Valproic acid–lamotrigine | Major | Increased elimination half-life of lamotrigine, leading to lamotrigine toxicity (fatigue, drowsiness, ataxia) and an increased risk of life-threatening rashes |

Associations that did not have any known interaction are not reported in the table

The mechanisms responsible for the development of drug-induced DRESS syndrome are not well known, and different factors have been postulated for its aetiology, including variations in drug metabolism and related metabolite accumulation. Theoretically, compounds with an aromatic structure have the potential to create epoxides during the metabolism pathway, particularly in the oxidation phase.

The reactivity of aromatic rings depends on the substituents of the rings and on an environmental reaction that can facilitate or inhibit this reaction of oxidation. The formation of reactive metabolites as epoxides is frequently related to occurrence of cancer, birth defects, tissue necrosis and hypersensitivity reactions. Indeed, many data have established the relation between epoxy resins and dermatitis/sensitization. However, the role of the epoxides differs significantly according to their molecular geometry, stability, reactivity and activity as substrates for enzymes that transform them (e.g. glutathione *S*-transferase, epoxy-hydrolase). Individual predisposition or additional factors (e.g. patients' acquired or pharmacogenetic variations) could be the cause of impaired detoxification and accumulation of reactive oxidative intermediates as epoxidic metabolites that could cause direct cellular toxicity or immune response.

When selecting the drugs with higher PRR values (allopurinol, phenobarbital, lamotrigine and sulfasalazine), we noted that the mechanisms of action for developing DRESS with phenobarbital and lamotrigine had already been discussed in the scientific literature [23]. Although metabolism by epoxidation cannot be excluded a priori for sulfasalazine (one of the two main metabolites of this active substance is 5-aminosalicylic acid, which could potentially be subject to epoxidation in unusual conditions), other metabolic pathways could be involved in the occurrence of serious adverse cutaneous reactions such as DRESS. Indeed, the second main metabolite of sulfasalazine is sulfapyridine, which is rapidly absorbed, hydroxylated and acetylated in the liver, and is subsequently excreted in the urine. The rate of acetylation in the liver is determined genetically, and slow acetylators are at increased risk of adverse reactions, such as hypersensitivity syndrome [24, 25].

Various oxidizing cytochrome P450 (CYP) enzymes, including CYP2C9, CYP2E1 and CYP3A4, can oxidize aryl amines to reactive metabolites [26], and sulfapyridine is converted into the unstable sulfapyridine hydroxylamine intermediate, which auto-oxidizes to nitroso-sulfapyridine.

Sulfapyridine and its metabolites contain an aromatic immunogenic structure like that of sulfamethoxazole.

Sulfonamide antibiotics are another common cause of drug-induced allergic reactions and are often associated with delayed cutaneous maculopapular eruptions, such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [27].

Metabolism also plays a key role in the occurrence of DRESS with allopurinol. Cell-mediated immunity (a type IV hypersensitivity reaction) to allopurinol and, more importantly, to its oxypurinol metabolite, is the mechanism involved in the pathogenesis of allopurinol-induced DRESS syndrome. The pathophysiology of allopurinol-associated DRESS syndrome seems to be related to accumulation of oxypurinol in patients with renal insufficiency. Hande and co-workers showed that the renal clearance of oxypurinol is directly proportional to the renal clearance of creatinine [28]. Accumulation of oxypurinol (the major metabolite of allopurinol) in renal insufficiency is considered a crucial factor for development of allopurinol hypersensitivity syndrome and may lead to tissue damage by toxic or immunological mechanisms [29].

As was confirmed by the results of our analysis, most active substances that cause DRESS hold a nitrogen-containing aromatic ring in their structure; therefore, it seems that not only an aromatic (benzene-like) structure but also a pyrimidine/pyridine-like structure or other aromatic heterocycles containing nitrogen might play a key role in the occurrence of DRESS.

### 4.1 Limitations and Strengths of this Study

The limitations of this study relate to its design, being a retrospective study based on a pharmacovigilance database. First, with the reliance on spontaneous reports, the cases of DRESS might have been under-reported. Nevertheless, this is the largest national case series ever published. Second, the reporting rate for causative drugs could have been biased. It is probable that the more frequently a medication is cited in the literature as being related to DRESS, the more likely it is that healthcare professionals will report relevant ADRs to NPN. Third, even if the reporting form guarantees good quality of the collected data, the form was not specifically designed to report cutaneous adverse reactions, and some important pieces of information—i.e. the ADR description and diagnosis, diagnostic examinations and therapeutic measures—were included as free-text fields in the reporting form. Therefore, our data were partially incomplete. Of note, we could not explore the role of patch-testing in DRESS diagnosis. Fourth, because of the structure of our database (see Online Resources 2 and 5), we could not exclude the possibility that the early DRESS occurrence that we noted in 20 of our 91 reports was due to medicine rechallenge. Last, a denominator was unavailable, so it was not possible to calculate the incidence of DRESS.

A point of strength of our analysis is that spontaneous reporting is a method able to provide essential information of clinical importance, although not comparable with personal clinical records or clinical trials. Analysis for a specific disease allows use of cumulative data and eventual detection of safety signals.

## 5 Conclusion

Using the Italian Medicines Agency NPN, we identified and described a large case series of patients with DRESS, a potentially fatal drug reaction that is increasingly being reported. We noted that the only common finding in all 91 patients included in this case series was the presence in the suspected drugs of an aromatic ring. We confirmed this presence by reviewing the medical literature published so far. Although the presence of an aromatic ring has previously been recognized as the possible cause of DRESS occurring with antiepileptic drugs, our analysis hypothesized, for the first time, that there is a possible association between the aromatic ring and the occurrence of DRESS.

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**Compliance with Ethical Standards**

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**Conflict of interest** Francesca Renda, Giovanni Landoni, Renato Bertini Malgarini, Alessandro Assisi, Maria Luisa Azzolini, Marta Mucchetti, Giuseppe Pimpinella and Luca Pani have no conflicts of interest that are directly relevant to the content of this study.

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