Intravenous glucocorticoid therapy for Graves' ophthalmopathy and acute liver damage: an epidemiological study

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Abstract
Objective: Intravenous glucocorticoid (i.v.GC) pulse therapy for Graves' ophthalmopathy (GO) can be associated with acute liver damage (ALD), which was roughly estimated to occur in ~1% of patients, with an overall mortality of 0.4%. The aim of this study was to evaluate the frequency of ALD after the introduction of a series of exclusion criteria and preventive measures.

Design: Retrospective evaluation of all consecutive patients candidate to i.v.GC over a period of 5 years.

Methods: The study includes 376 GO patients candidate to i.v.GC. Several liver tests were performed before, during, and after i.v.GC. To prevent ALD morbidity and mortality, the following measures were applied: i) exclusion of patients with active viral hepatitis and/or severe liver steatosis; ii) reduction in the GC dose, frequency, and number of pulses; and iii) administration of oral GC after i.v.GC, and also during i.v.GC in patients positive for nonorgan-specific autoantibodies (to prevent autoimmune hepatitis due to immune rebound). ALD was defined as an increase in alanine aminotransferase ≥ 300 U/l.

Results: A total of 353 patients were given i.v.GC and 23 were excluded for various conditions. ALD was detected in 4/376 patients candidate to i.v.GC, resulting in a morbidity of 1.06%. One patient recovered spontaneously and three after additional treatment with oral GC, given to re-establish immune suppression in the suspect of an autoimmune hepatitis.

Conclusions: ALD related to i.v.GC is a relatively rare adverse event. Provided an accurate selection of patients and a series of preventive measures are applied, i.v.GC is a safe treatment for the liver.

Introduction
High-dose, intravenous glucocorticoid (i.v.GC)-pulse therapy was introduced for the treatment of Graves' ophthalmopathy (GO) in 1987 (1), becoming quite popular thereafter and, at least in some countries, replacing to a large extent the oral route of administration of GC (2, 3). Several studies have shown a greater effectiveness of i.v.GC compared with oral GC, as well as a lower prevalence of common side-effects such as high blood pressure, diabetes, cushingoid features, urinary infections, gastritis, and psychic disturbances (2, 3). However, since its introduction in the clinical practice, unlike oral GC, i.v.GC has been associated with a few cases of acute liver damage (ALD), some of which lethal (4, 5, 6, 7, 8, 9). Thus, following the report of two cases of lethal ALD in patients with nonorgan-specific autoimmune diseases (systemic lupus eritematosus and dermatomyositis) (10), in 2000 Weissel & Hauff (4) reported a case of deathly, acute liver failure in a woman with GO.
Liver damage associated with i.v.GC can reflect three possible pathogenetic mechanisms. First, GC may exert a direct damage on liver cells (5, 10, 11), in which case one would expect a dose-dependence of ALD extent and outcome. Second, following the immune suppression induced by GC, a sudden reactivation of the immune system, the so called ‘rebound phenomenon’, may precipitate an autoimmune hepatitis in predisposed individuals (5, 6, 7). Third, after a previous exposure to hepatitis B (HBV) and/or hepatitis C (HCV) viruses, immune suppression due to GC may reactivate HBV or HCV. The latter, as determined by liver ultrasound, is expected to represent risk factors for a possible direct toxic effect of GC (10, 11); ii) reduction of the GC dose, frequency, and number of pulses; these measures were based on the knowledge that GC may exert a direct toxic effect on liver cells, which is expected to be dose-dependent (10, 11); and iii) administration of oral GC after i.v.GC, in order to prevent an autoimmune rebound and a consequent autoimmune hepatitis, as described in at least two patients given i.v.GC (6, 7).

The aim of the present study was to evaluate retrospectively the frequency of ALD in a series of consecutive patients with GO candidates to i.v.GC, in whom the above mentioned selection criteria and preventive measures were applied.

**Subjects and methods**

**Study design and patients**

The design of the study was to determine the frequency of ALD in all consecutive GO patients candidate to i.v.GC with a moderate-to-severe active GO, defined based on the criteria proposed by the European Group on Graves’ orbitopathy (EUGOGO) (15), where the above mentioned selection criteria and preventive measures were applied. Signed informed consent was obtained from all patients.

**Evaluation before i.v.GC**

Approximately 2 weeks before treatment, all patients underwent the following evaluation: i) routine blood tests, including, among others, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, aspartate (AST) and alanine (ALT) aminotransferase, alkaline phosphatase (ALP), gamma-glutamyl transferase (γGT), total and direct bilirubin; ii) thyroid function tests, including free tri-iodothyronine, and thyrotropin; iii) serum markers of exposure to HBV and HCV; iv) serum autoantibodies known to be associated with autoimmune hepatitis (12, 13, 14), namely anti-nuclear (ANA), anti-mitochondrial (AMA), anti-centromeric, anti-liver-kidney-microsomal (LKM), and anti-smooth muscle antibodies (ASMA); and v) liver ultrasound.

**Regimen of i.v.GC treatment and follow-up procedures**

Patients were scheduled to receive 12 weekly infusions of methylprednisolone acetate (MPA) at a dose of 15 mg/kg of body weight for the first four infusions and of 7.5 mg/kg of body weight for the last eight infusions. Twenty-four patients were given the treatment twice for persistence or relapse of moderate-to-severe active GO, not before 12 months from the previous course. Beginning on the day after the last infusion of MPA, patients were given oral prednisone, starting at a dose of 40 mg every other day, which was tapered every 10 days to be withdrawn after 50 days. The patients who had positive tests for nonorgan-specific autoantibodies were also given oral prednisone 40 mg every other day beginning on the day after the third infusion of MPA, in order to prevent autoimmune rebound. This treatment was continued until the end of i.v.GC, after which the same protocol of oral prednisone used for the remaining patients was started.

AST, ALT, ALP, GT, and total and direct bilirubin were scheduled to be measured every 2 weeks during i.v.GC, as well as every 2 weeks after i.v.GC, up to 3 months after the end of treatment; then they were measured monthly up to 6 months after the end of treatment.

In order to prevent GC-induced osteoporosis, postmenopausal women were given alendronate 70 mg/week...
up to 3 months after completion of oral GC. No side-effects of alendronate were recorded. No calcium or vitamin D supplantations were given. To prevent GC-induced gastritis, all patients were given omeprazole 20 mg/day up to 2 weeks after completion of oral GC.

End points
The primary end point of the study was the frequency of a clinically relevant liver damage, which was defined as an increase in ALT ≥ 300 U/l (16, 17, 18). ALT, rather than AST, was chosen because it is more specific to the liver. In patients with ALD, we calculated the revised International Autoimmune Hepatitis Score, developed by the International Autoimmune Hepatitis Group (IAHG) (19), which is based on the following parameters: i) gender; ii) ALP/ALT ratio; iii) serum globulins or IgG increase; iv) presence or absence of ANA, ASMA, or LKM; v) presence or absence of AMA; vi) presence or absence of hepatitis viral markers; vii) history of illicit drug use; viii) history of alcohol abuse; ix) histological findings compatible or not with autoimmune hepatitis; and x) presence of other autoimmune diseases.

The secondary end point of the study was the relationship, if any, between liver damage and the following variables: gender; age; cumulative MPA dose; thyroid status before i.v.GC; obesity (a BMI ≥ 30) before i.v.GC; BMI values before i.v.GC; clinically overt previous liver diseases of any type (comprising viral hepatitis of any type, toxic hepatitis, alcohol-related acute or chronic liver disorders); previous exposure to HBV or HCV; positive tests for nonorgan-specific autoantibodies; administration of prednisone during i.v.GC; liver steatosis before i.v.GC (as detected by ultrasound); diabetes before i.v.GC; hypertension before i.v.GC; hyperlipemia before i.v.GC; and total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides values before i.v.GC.

Results
Of the 376 patients scheduled to undergo i.v.GC, 23 were not given the treatment. One patient was excluded because of an alcohol-related cirrhosis; seven because they had an active, chronic, viral hepatitis, four HBV- and three HCV-related; 11 because they had a severe liver steatosis (a marked increase of liver echogenicity), as assessed by ultrasound; three patients were excluded because of an uncontrolled hypertension and one because of a concomitant Herpes Zoster infection. These 23 patients were treated with orbital radiotherapy and 17 of them also with orbital decompression.

The remaining 353 patients were treated with i.v.GC, 24 of whom were treated twice for persistence or relapse of active GO. Treatment was completed in 343 patients, whereas it was stopped in ten patients for the following reasons: stroke (one patient), high blood pressure (two patients), unrelated lung embolism (one patient), gastritis (one patient), optic neuritis requiring orbital decompression (one patient); as detailed below, in two patients i.v.GC was stopped because of an overt ALD, and in two because of an increase in the levels of liver enzymes, yet not sufficient to meet the criteria for ALD (ALT values < 300 U/l).

The cumulative dose of MPA was 7.5 ± 1.2 g, ranging from 3.8 to 13.3 g. As mentioned previously, in addition to MPA, all patients were given oral prednisone after i.v.GC and 83 patients positive for nonorgan-specific autoantibodies were given oral prednisone also during i.v.GC. Therefore, by summing the MPA dose and the dose of prednisone, the cumulative GC dose was 8.0 ± 1.3 g in patients without detectable nonorgan-specific autoantibodies and 9.2 ± 1.1 g in patients with detectable nonorgan-specific autoantibodies. However, there was no statistical difference in the MPA dose between these two groups (P = NS by t test).

An overt ALD, namely a serum ALT value ≥ 300 U/l, was detected in four patients, which, applying the intention-to-treat criterion, resulted in a morbidity of 1.06% (4/376 patients). Individual features of these patients are reported in Tables 1 and 2 as well as in Fig. 1.

In two cases, ALD occurred during i.v.GC, which, as reported above, was consequently interrupted; in the other two cases ALD was observed shortly after i.v.GC. All four patients were asymptomatic. One of them (LP) had positive tests for HBV exposure (detectable anti-HBs and anti-HBc antibodies), but with no signs of active hepatitis (negative HBs antigen and HBV DNA), prior, during, and up to 6 months after i.v.GC, and normal liver ultrasound. HBV markers were negative in the remaining three patients as were markers of HCV exposure in all patients with ALD. In these four patients, we also assessed serum markers of exposure to cytomegalovirus and Epstein Barr virus, which were negative in all cases.

All patients with ALD had a mild steatosis at liver ultrasound (a slight increase of liver echogenicity). In one case (LP), liver enzymes returned spontaneously within the normal range and the patient remained completely asymptomatic (Tables 1 and 2, Fig. 1A). In the remaining three patients, an autoimmune hepatitis was suspected in spite of the absence of a liver biopsy, and patients were
treated with oral GC to re-establish immune suppression (Tables 1 and 2, Fig. 1B, C, D). In two of these three patients, the suspect of an autoimmune hepatitis was based on the fact that they had positive tests for nonorgan-specific autoantibodies, namely ASMA (patient AR, Table 1) and ANA (patient MR, Table 1), which, as mentioned above, are known to be associated with autoimmune hepatitis (5, 7); these two patients had been given oral GC during the interpulse periods (Table 2). Once ALD was detected, in both cases during i.v.GC, both i.v.GC and oral GC were stopped, but, because ALT increased further, they were re-administrated oral GC to re-establish a certain degree of immune suppression, which was followed by a reduction up to normalization in liver enzymes (Table 2, Fig. 1B and C).

In the fourth patient (Fig. 1D), ALD was observed after the end of i.v.GC. Because of the appearance of ALD immediately after the reduction in the dose of oral i.v.GC, an autoimmune hepatitis was suspected, in spite of the negative tests for autoimmune hepatitis-associated autoantibodies (Table 1). Therefore, higher doses of oral GC were given, which, as in the previous two patients, was followed by a reduction up to normalization of liver enzymes (Table 2, Fig. 1D). Given the limitation of the absence of a liver biopsy, we calculated the revised International Autoimmune Hepatitis (19), which was three in patient LP, eight in patients AR and MR, and six in patient GM, supporting an autoimmune pathogenesis in the latter three patients.

Overall, nonorgan-specific autoantibodies that can be associated with autoimmune hepatitis were detectable in 83 patients (23.5%), two of whom (2.4%) had an ALD. The frequency of ALD in patients without nonorgan-specific autoantibodies was only 0.68% (2/293 patients), but the difference in patients with nonorgan-specific autoantibodies was not statistically significant ($P = NS$ by Fisher’s exact test).

As mentioned previously, in two additional patients there was a mild increase in ALT during i.v.GC, and i.v.GC was stopped because of this reason. The increase in ALT

<p>| Table 1 | Demographical features, associated conditions, and serum findings before treatment in four patients with Graves’ ophthalmopathy who developed an acute liver damage during or following i.v. glucocorticoid pulse therapy (i.v.GC). |</p>
<table>
<thead>
<tr>
<th>ID</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Thyroid status</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Hyperlipidemia</th>
<th>BMI</th>
<th>Liver steatosis</th>
<th>NOS Ab</th>
<th>Virus markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP</td>
<td>Male</td>
<td>61</td>
<td>Eu</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>27</td>
<td>Yes</td>
<td>None</td>
<td>HBV&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>AR</td>
<td>Female</td>
<td>78</td>
<td>Eu</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>19</td>
<td>Yes</td>
<td>ASMA 1:80</td>
<td>None</td>
</tr>
<tr>
<td>MR</td>
<td>Female</td>
<td>53</td>
<td>Eu</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>19</td>
<td>Yes</td>
<td>ANA 1:320</td>
<td>None</td>
</tr>
<tr>
<td>GM</td>
<td>Male</td>
<td>46</td>
<td>Eu</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>24</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

NOS Ab, nonorgan-specific autoantibodies; Eu, euthyroid; ASMA, anti-smooth muscle autoantibodies; ANA, anti-nuclear autoantibodies.

<sup>a</sup>HBV: hepatitis B virus. This patient had detectable anti-HBs and anti-HBc antibodies, but with no signs of active hepatitis (negative HBs antigen and HBV DNA), prior, during, and up to 6 months after i.v.GC, and normal liver ultrasound.

<p>| Table 2 | Details on i.v. glucocorticoid (i.v.GC) pulse therapy and on the features of acute liver damage (ALD) in four patients with Graves’ ophthalmopathy. |
| --- | --- | --- | --- | --- | --- | --- | --- |</p>
<table>
<thead>
<tr>
<th>ID</th>
<th>MPA dose (gr)</th>
<th>Number of MPA pulses</th>
<th>Oral GC after i.v.GC</th>
<th>Oral GC during i.v.GC</th>
<th>Time of diagnosis (weeks)</th>
<th>Duration of ALD (weeks)</th>
<th>ALT peak (U/l)</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP</td>
<td>8</td>
<td>12</td>
<td>Yes</td>
<td>No</td>
<td>After the beginning of i.v.GC</td>
<td>13</td>
<td>1</td>
<td>14.3</td>
<td>357</td>
</tr>
<tr>
<td>AR</td>
<td>6.35</td>
<td>11</td>
<td>Yes</td>
<td>Yes</td>
<td>After the end of i.v.GC</td>
<td>8.2</td>
<td>–</td>
<td>11.3</td>
<td>490</td>
</tr>
<tr>
<td>MR</td>
<td>3.82</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>6.3</td>
<td>–</td>
<td>20</td>
<td>325</td>
<td>Stop i.v.GC and oral GC</td>
</tr>
<tr>
<td>GM</td>
<td>12.5</td>
<td>18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>14</td>
<td>2.3</td>
<td>13.4</td>
<td>415</td>
<td>Higher dose oral GC</td>
</tr>
</tbody>
</table>

MPA, methylprednisolone acetate; ALT, alanine aminotransferase.

<sup>a</sup>Patient GM was treated with two separate courses of i.v.GC.
was not sufficient to meet the criteria for ALD, being the highest value detected 145 U/l. In both these cases, liver enzymes returned spontaneously within the normal range. In theory, these patients may have developed an ALD according to our criteria if treatment was continued, in which case, however, ALD morbidity would have increased only up to 1.26%.

Presumably because of the very low frequency of ALD, it was not possible to establish a statistical relationship between liver damage and gender, age, MPA dose, thyroid status, obesity, BMI, clinically overt previous liver diseases, exposure to HBV or HCV, positive tests for nonorgan-specific autoantibodies, administration of interpulse prednisone, liver steatosis, diabetes, hypertension, hyperlipemia, cholesterol, and triglycerides.

As expected, we observed also adverse events other than ALD during i.v.GC. In addition to five patients reported previously, in whom i.v.GC was stopped because of adverse events unrelated to GO (one stroke, two high blood pressure, one lung embolism, and one gastritis), we observed one case of overt diabetes mellitus. The patient was treated with insulin and recovered completely after the end of i.v.GC. We observed mild increases in blood glucose in another 23 patients, which however did not require specific treatment.

**Discussion**

The observation of several cases of ALD during or after i.v.GC in patients with GO has raised doubts on the safety of this type of treatment (4, 5, 6, 7, 8). Obviously, this is a major issue, considering that GC in general, and more recently i.v.GC, are by far the most common treatment modality for moderate-to-severe and active GO (2, 3). The exact frequency of ALD and its risk factors are not known. However, beginning in 2008 we established empirically a series of exclusion criteria and preventive measures. The aim of this study was to determine retrospectively ALD morbidity and mortality after the introduction of such measures in a relatively large series of consecutive patients with GO candidate to i.v.GC.

Overall, we observed four cases of ALD out of 376 patients candidate to i.v.GC, which, applying the intention-to-treat criterion resulted in a 1.06% morbidity. In two additional patients, liver enzymes increased during i.v.GC, but not to a sufficient extent for ALD criteria.
to be met. Nevertheless, even if we included these two patients in the ALD group, morbidity would not have increased much (1.26%).

In our previous report (5), we had observed seven cases of ALD in ~800 patients treated with i.v.GC, resulting in a morbidity of ~0.9%. However, the two studies cannot be compared in terms of morbidity, because in our previous study liver enzymes were not measured systematically in all patients, and therefore the frequency of ALD was likely greater. Whereas in our previous study, an ~0.4% of ALD-related mortality was detected (5), in this study no deaths were recorded for ALD, and all patients in whom ALD was diagnosed recovered completely, either spontaneously or after treatment. Therefore, the preventive measures applied here were likely associated with the abolishment of ALD mortality.

As mentioned previously, liver damage associated with i.v.GC can be due to three possible mechanisms: i) a direct damage on liver cells exerted by GC (5, 10, 11), which should be dose-dependent; ii) an autoimmune hepatitis due to immune rebound (5, 6, 7); and iii) a viral reactivation (5).

Of the original 476 patients candidate to i.v.GC, 23 were excluded, most of whom for liver-related conditions. Obviously it is not possible to establish whether exclusion of these patients had an impact on the frequency of ALD. On the other hand, it would not have been ethically acceptable to give i.v.GC to patients with conditions which, although yet not proven as certain risk factors, may in theory precipitate ALD.

As mentioned previously, ALD due to a direct toxic effect of drugs should be dose-dependent, because of which the dose of MPA and the number of administration were reduced after the observation of the first cases of ALD. In a recent survey among members of the European Thyroid Association (8), as well as in a recent meta-analysis (3), it was shown that fatal adverse events, including ALD, are quite unlikely when cumulative MPA doses of 8 g or less are administered. Concerning ALD, all patients with a fatal outcome reported in the literature were given MPA doses >8 g (3, 4, 5, 8). The treatment regimen used here employed an average MPA cumulative dose of 7.5 g and the 24 patients given cumulative doses >8 g had been treated twice for persistence or relapse of moderate-to-severe GO, with courses that were separated from one another by at least 1 year. Cumulative doses in these patients ranged from 8.5 to 13.3 g and of the four cases of ALD reported here, one belonged to this small subgroup (MPA cumulative dose: 12.5 g). Coupled with the data of the literature (3, 4, 5, 6, 7, 8), our observations seem to support a role of the cumulative MPA dose on the occurrence of ALD and the fact that a reduction in the MPA dose below 8 g, as applied here, somehow prevents the occurrence of ALD, considering that, as discussed below, in three out of four cases the pathogenesis of ALD was possibly autoimmune.

As just mentioned, the most frequent mechanism that apparently caused ALD seemed to be autoimmune, likely due to the so-called immune rebound, namely the sudden reactivation of the immune system following GC-induced immune suppression. In the literature, there are at least two case reports of a clear-cut autoimmune ALD induced by i.v.GC in patients with GO (6, 7). These two patients were treated with GC themselves, in order to re-establish a certain degree of immune suppression, with a favorable outcome of ALD. In order to predict and possibly prevent the risk of autoimmune hepatitis, patients were tested for nonorgan-specific autoantibodies known to be related to autoimmune hepatitis (12, 13, 14), and, in addition, they were all given oral GC after the end of i.v.GC to prevent immune rebound. Furthermore, patients who had positive tests for nonorgan-specific autoantibodies were given oral GC also during i.v.GC, in order to prevent immune rebound between i.v.GC pulses. Although the frequency of ALD did not differ statistically in relation to the presence of nonorgan-specific autoantibodies, it seemed to be greater in positive patients, thereby raising the need for further studies in a large series of patients to determine whether nonorgan-specific autoantibodies represent a true risk factor, which could not be established here presumably because of the rarity of ALD. Because they were given oral prednisone, the cumulative GC dose was greater in patients positive for nonorgan-specific autoantibodies. However, this was the unlikely cause of the apparent, yet not significant, greater frequency of ALD in these patients, as the cumulative GC dose in this group did not differ statistically from that given to patients without detectable nonorgan-specific autoantibodies. Obviously, it is not possible to establish whether the administration of oral GC after i.v.GC and eventually during GC prevented autoimmune ALD, as these should be compared with a patient population not given oral GC, provided this would be ethically acceptable.

Besides nonorgan-specific autoantibodies, the role of which has still to be proven, we could not determine other potential risk factors for ALD, clearly because of its relatively low frequency.

A limitation of this study was the absence of a formal control group. Thus, although the potential risk factors we considered in designing the exclusion criteria and...
preventive measures were reasonable and somehow supported by the available literature (3, 4, 5, 6, 7, 8, 10, 11), there are no available studies that have identified with certainty ALD risk factors with a sensitivity and a specificity sufficient enough to be applied in the clinical practice. To some extent, this was overcome by the comparison with our previous study (5), at least concerning mortality, although a control group in which the exclusion criteria and preventive measures used in this series of patients had not been applied would have given a final answer. However, this was not possible to realize, on one hand because this was not planned as a prospective study, on the other hand, and most importantly, because it would not have been ethically acceptable not to apply the exclusion criteria and preventive measures used here, even if empirical, in a hypothetical control group, considering that ALD has caused four known deaths in the past (4, 5).

One of the preventive measures we applied was to exclude patients with severe liver steatosis at ultrasound. However, because liver steatosis is a common finding in the apparently healthy population, more specific techniques, such as fibroscan (20), may allow a better selection of patients, to determine which further studies are required.

Based on our findings, we can conclude that ALD is a relatively rare adverse event during or after i.v.GC for GO, affecting about 1% of patients candidate to treatment, and with no mortality using the preventive measures applied here. Therefore, unlike in the past, i.v.GC can be considered as a safe treatment for the liver, provided an accurate selection of patients and the previously mentioned preventive measures are applied. Our practical suggestions are as follows: i) liver screening before i.v.GC; ii) exclusion of patients with cirrhosis, chronic HBV or HCV hepatitis, or severe liver steatosis; iii) oral GC after GC, and also during GC in patients with positive nonorgan-specific autoantibodies; iv) MPA cumulative doses ≤8 g; v) monitoring of liver enzymes during and after i.v.GC; and vi) prompt treatment of autoimmune hepatitis.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
Supported by a grant from MIUR (Ministero dell’Istruzione, dell’Università e della Ricerca Scientifica) (2004068078 to M Marinò).

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Received 19 August 2014

Revised version received 27 October 2014

Accepted 1 December 2014