Idiopathic recurrent pericarditis (IRP) is a common and frustrating complication of acute idiopathic pericarditis and is characterised by the reappearance of chest pain during convalescence or after recovery from the initial attack. IRP is one of the possible manifestations of pericardial disease, which covers a wide clinical spectrum and includes, among others, acute and recurrent pericarditis, cardiac tamponade, constrictive and effusive-constrictive pericarditis, as well as specific forms of the disease. A fundamental precondition for the diagnosis of recurrent pericarditis is a history of a documented first episode of acute pericarditis. Clinical manifestations of pericarditis include chest pain, pericardial rub, a series of characteristic ECG changes in the PR interval, ST segment and T wave, with or without pericardial effusion. According to the 2004 European Guidelines, the presence of at least two of these four findings is a necessary criterion for diagnosis.

Pericardial involvement is observed in a variety of diseases, mainly infections and systemic disorders. However, with the standard laboratory tests an aetiopathological approach to acute pericarditis is seldom possible, especially if molecular biological techniques are not used. In consequence, with current diagnostic algorithms, in immunocompetent patients and in developed countries, 80-90% of cases of acute pericarditis will end up being classified as idiopathic. Most probably, in those cases the underlying cause is a non-apparent viral infection, so that for practical purposes the terms acute “viral” and “idiopathic” pericarditis can be considered to represent the same entity.

IRP is the most frequent complication of acute idiopathic pericarditis. It includes two subcategories: the intermittent type, in which the interval between the acute episode and recurrence is greater than 6 weeks; and the incessant type, in which the discontinuation (or dose reduction) of anti-inflammatory medication causes a relapse of the symptoms within less than 6 weeks from the acute episode. Recurrence after an acute episode of pericarditis has been described in 8-80% (mean ~24%) of cases in clinical series with >40 patients, although the type of recurrence (incessant or intermittent) was not specified.

The clinical picture of recurrences is similar to that of the acute episode, but the clinical manifestations are usually milder. However, it still has a negative impact on the patient’s quality of life, while also being a matter of concern for the treating physician. The number of recurrences and the intervals between them show wide variations between patients, although the recurrences tend to vanish with time. The first recurrence is followed by others in about 50% of cases. Although a recurrence following an acute episode usually occurs in the short term, within the next few months, some patients show recurrence even after remaining free of symptoms for a long time.
The criteria for the diagnosis of IRP begin with the history of a documented first episode of acute pericarditis in combination with chest pain. In addition, there must also be at least one of the following findings: fever, pericardial rub, ECG signs compatible with acute pericarditis (i.e. widespread saddle-shaped or concave upward ST segment elevation), pericardial effusion on echocardiographic examination, and an increase in white blood cells, erythrocyte sedimentation rate, or C-reactive protein (CRP).12

It should be noted that recurrent pericarditis does not include symptomatic pericardial effusion with normal CRP levels, or asymptomatic chronic pericardial effusion, whose clinical significance and treatment are not presently known.3

Pathogenetic mechanisms

The pathogenetic mechanisms that have been implicated in the recurrence (or recurrences) of pericarditis include the following: i) inadequate dose and/or duration of anti-inflammatory or corticosteroid medication, especially in cases where the underlying disorder is an autoimmune disease; ii) early administration of corticosteroids, causing augmented viral DNA/RNA replication in the pericardial tissue leading to increased viral antigen exposure; iii) reinfecion; iv) exacerbation of an underlying connective tissue disease.2,3,6 Finally, there are indications that genetic factors may also be responsible for recurrences.13,14 Specifically, occasional cases have been described with an autosomal dominant inheritance (with incomplete penetrance) as well as another sex-linked form.14,15 With regard to the major histocompatibility complex, the antigens that have been found with increased frequency in patients with recurrence are HLA B14, DRBI*01, DQB1*0202, A*02 and Cw*07.16,17 Also, in a study of patients with recurrent pericarditis the incidence of idiopathic pericarditis in the familial environment was 10%.18 However, further studies are needed of the possible contribution of the major histocompatibility complex and other candidate genes to the recurrence of the disease.18

Based on available data from continuing research, although none of the above mechanisms has been ruled out as a contributory factor, IRP today tends to be viewed more and more as an autoimmune disease, or at least an intermediate state between the two extremes of infection and autoimmunity.3,16,18,19 Indeed, in the acute phase of idiopathic pericarditis the pericardial inflammation is attributed to a direct insult to the pericardium from the responsible micro-organism.3 Subsequently, during the phase of viral proliferation, a cellular and humoral immune response is elicited, with the result that the initial infectious disease takes on autoimmune characteristics.3,7

Indications of the autoimmune nature of IRP are provided by the presence in pericardial fluid of proinflammatory cytokines, such as interleukin 6 (IL-6), interleukin 8 (IL-1) and interferon γ (INF-gamma), which notably are not detected in the serum, a fact that suggests a localised inflammatory reaction.5,20 Recently, the term “autoinflammatory” has been introduced to medical terminology to describe conditions characterised by recurrent episodes of apparently unprovoked serosal inflammation, leukocytosis, and familial occurrence (a typical example is familial Mediterranean fever).19 These disorders are often due to a disturbance of the mechanisms of innate immunity, and interleukin 1 (IL-1) appears to play a central role in their manifestations.19,21 It seems that some subgroups of patients with IRP satisfy the above criteria and in these cases the pericardial inflammation is probably a manifestation of a yet undiagnosed autoinflammatory disease.19 As regards the serum of patients with recurrent pericarditis, antinuclear antibodies (ANA) are detected in a percentage of up to 59%, much higher than in healthy volunteers (9.8%).16,22 However, moderately elevated titres (>1/160) have been found in a smaller percentage (15%), mainly in patients with known rheumatological disease.16,22 The presence of ANA does not appear to have prognostic significance, either with regard to the complication rate, or for the later manifestation of rheumatological disease.22 Autoantibodies of rheumatoid factor and anti-Ro(SSa) type have also been detected in the serum of IRP patients at rates of 4-15% and about 4%, respectively.16,22 The autoimmune nature of IRP is reinforced even further by the good response observed following the administration of anti-inflammatory and/or immunosuppressant medications, as well as by the manifestation during the long-term follow up of these patients of diseases with a documented autoimmune aetiology, such as rheumatoid arthritis and Sjögren’s syndrome.16

Taking into account the above observations, we can conclude that there are strong indications that the immune system plays a central role in the pathogenesis of IRP, although there is no definite proof of this at the present time.

Therapeutic management

As in cases of acute idiopathic pericarditis, physical
activity in patients with IRP must be limited until the complete remission of chest pain.\textsuperscript{2,4,23} Medication includes non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, occasionally corticosteroids, and rarely immunosuppressant drugs.\textsuperscript{2,3,23} Finally, in refractory cases, pericardectomy should be considered.\textsuperscript{2}

**NSAIDs**

Protocols for the administration of NSAIDs do not actually differ from those used in acute idiopathic pericarditis. In IRP, too, high doses of NSAIDs are considered the cornerstone of treatment. Most usually, aspirin is given in a daily dose of 2-4 g administered every 4-6 hours, ibuprofen 1.2-3.2 g daily every 6-8 hours, and indomethacin 75-225 mg daily, also every 6-8 hours, with a similar efficacy as regards pain relief and suppression of inflammation (85-90\% success).\textsuperscript{2,4,8} It should be noted that NSAIDs have no effect in preventing further recurrences, or other complications such as cardiac tamponade and constrictive pericarditis.\textsuperscript{4} In cases where the chest pain is not relieved within 2 weeks, another NSAID may be given, although nowadays, as is reported below, there are a number of alternative strategies.\textsuperscript{4} Moreover, given the high efficacy of NSAIDs, if symptoms are not relieved within 1 week of treatment at recommended doses, the possibility of a specific aetiology for the disease should be considered and investigated.\textsuperscript{5}

Of the abovementioned anti-inflammatory agents, ibuprofen is used most often because of its low rate of side effects, its beneficial action on coronary flow, and the wide range of recommended doses for the drug.\textsuperscript{2,4} Indomethacin should be avoided in patients with coronary artery disease, because of its negative effect on coronary flow.\textsuperscript{24} In cases with severe chest pain, some experts recommend the initial intravenous administration of ketorolac (NSAID agent structurally similar to indomethacin) in a dosage of 30 mg every 6 hours for a short time, after which it is replaced by an orally administered NSAID.\textsuperscript{23}

As regards the duration of therapy in cases of recurrence, in practice there are no guidelines based on evidence-based medicine. The duration of administration may range from days to weeks (probably with progressive NSAID dose reduction), according to the severity of the clinical picture and the response to treatment.\textsuperscript{2} In the CORE study (where colchicine was used) the duration of aspirin treatment in patients with a first episode of IRP was 800 mg orally every 6 or 8 hours for 7-10 days with gradual tapering over 2-3 weeks.\textsuperscript{12} In any case, administration should not be stopped before the achievement of complete pain relief, restoration of indexes of inflammation (erythrocyte sedimentation rate and CRP) to normal levels, and probably complete absorption of pericardial fluid.\textsuperscript{2,23}

Finally, it should not be forgotten that, with NSAIDs, proton pump inhibitors must be co-administered for gastroprotection.\textsuperscript{2} Also, in patients who are taking anticoagulants orally for any reason, administration of either ibuprofen or nimesulide is recommended, these being the safest drugs, or corticosteroids in low doses.\textsuperscript{10}

**Colchicine**

Since as long ago as 1987 there have been indications that colchicine could be used for the prevention of recurrences of acute pericarditis.\textsuperscript{25} However, the first randomised, prospective trial to evaluate the efficacy and safety of colchicine was carried out in 2005 (CORE).\textsuperscript{12} In that study, 84 patients with a first recurrence were randomised either to aspirin 800 mg orally every 6 or 8 hours for 7 to 10 days, or treatment with aspirin combined with colchicine, 1.0 to 2.0 mg the first day and then a maintenance dose of 0.5 to 1.0 mg daily for 6 months. Where there was a contraindication for aspirin administration, prednisone was given at 1.0 to 1.5 mg/kg per day for 4 weeks and then was gradually tapered. In this trial, during a 6-month follow-up period, colchicine halved the incidence of recurrence (24.0\% vs. 50.6\%, p=0.02), as well as drastically reducing the rate of persistence of chest pain beyond 72 hours (10\% vs. 31\%, p=0.03), without showing any severe adverse effects.

In the 2004 guidelines, i.e. before the publication of the CORE trial, based on existing experience and the results of relevant non-randomised trials, colchicine received a Class I recommendation, with Level of Evidence B, for the treatment of recurrent pericarditis.\textsuperscript{2,26} The suggested treatment regimen in those guidelines is 2 mg per day for 1-2 days and then 1 mg per day, with no mention of the recommended duration of therapy.\textsuperscript{2}

According to the CORE trial protocol, since it dealt with first recurrences, colchicine was to be given for 6 months. In the case of repeated recurrences, however, some experts recommend administration of the drug for 12-24 months after the last recurrence, followed by progressive tapering to termination.\textsuperscript{10,26,27} As regards the safety of colchicine, as mentioned above, the CORE trial recorded no serious adverse effects.\textsuperscript{12} The most usual adverse effect was diarrhoea, which required interruption of the medication in 7\%
of cases. Another common adverse effect of colchicine is a moderate increase in transaminases (7% of cases). It should be borne in mind that the CORE study excluded patients with serum creatinine >2.5 mg/dl, elevated transaminases to >1.5 times the upper normal limit, and known myopathy or elevated creatine kinase (CPK). A loading dose of 1 mg followed by a maintenance dose of 0.5 mg is reserved for patients with body weight <70 kg and those aged >70 years. Colchicine is contraindicated in severe hepatic dysfunction and when the values of creatinine clearance are below 20 ml/min. At clearance rates of 35-49 ml/min the recommended dose is 0.5-0.6 mg per day, while for clearance 10-34 ml/min the recommended dose is 0.5-0.6 mg every 2-3 days. It must be remembered that colchicine is an antimitotic drug and is therefore contraindicated during pregnancy. However, in patients with familial Mediterranean fever colchicine, even after prolonged administration, had no effects on male or female fertility, outcome of pregnancy, foetal development or development after birth.

Corticosteroids

According to the current guidelines, administration of corticosteroids is reserved for patients with a poor general condition, in cases of NSAID failure, and in frequent, hard-to-control recurrences (Class IIa recommendation, Level of Evidence C). The guidelines recommend a dose of 1-1.5 mg/kg prednisone for at least 1 month, tapered over a three-month period (total predicted duration of therapy about 4 months). Each reduction in dosage requires that the patient be asymptomatic, with CRP within normal limits. In the case of recurrence of symptoms, an increase up to the minimum effective dose is recommended, followed again by dose tapering over 3 months. In the latter case, towards the end of the reduction protocol the addition of an NSAID or colchicine is recommended. However, there is also the expert view from referral centres that in the case of symptom recurrence an increase in corticosteroid dosage should be avoided as far as possible, and that the symptoms should be controlled by the administration of an NSAID. The critical dosage for recurrence during the dose reduction procedure appears to be 25 mg prednisone.

It should be noted that, in the two randomised, prospective studies COPE and CORE, which examined the efficacy of colchicine in preventing recurrence of a first episode of pericarditis (COPE) or a subsequent recurrence after the first (CORE), the administration of corticosteroids proved to be an independent factor for recurrence, with odds ratio (OR) 4.3 (p=0.024) and 2.89 (p=0.04), respectively. Similarly, in a multi-centre observational study the previous administration of corticosteroids was shown to be an independent factor for disease recurrence after colchicine administration (OR 6.68), thus reducing the efficacy of the latter drug. A common error that often makes corticosteroid therapy appear ineffective is the administration of very small doses with rapid tapering of the dosage of the drug.

The recommendation of high doses of corticosteroids for pericardial diseases in the recent guidelines (1-1.5 mg/kg), is striking when one compares them with autoimmune conditions, such as collagen disease, which have been documented as being controlled with much smaller doses (0.1-0.5 mg/kg). In addition, it is troubling that the prednisone dosage recommended by the guidelines is drawn largely from a single-centre retrospective study with only 12 patients! The important issue of the optimum corticosteroid dose for patients with IRP was re-examined in a recent retrospective study that compared high and lower doses of corticosteroids. That study enrolled 100 patients with recurrent pericarditis—idiopathic, autoimmune (including post-pericardectomy syndrome) and recurrent pericarditis in the setting of connective tissue diseases. About half of the patients (49) were given low doses of prednisone (0.2-0.5 mg/kg/day), while the others received a high dose (1 mg/kg/day). The initial dosage was maintained for 1 month and then tapered, based on the predetermined protocol given in Table 1. In this study it was found, paradoxically, that the recurrence rate was about double in the patients taking the high dosage (64.7% vs. 32.6%, p=0.002), while the incidence of adverse effects was also higher in that group of patients (23.5% vs. 2%, p=0.002), as would be expected. Based on this important observation, the practice of administering high doses of prednisone in such cases should probably be reviewed. In any case, until further data become available, the choice of lower doses should be considered as a reasonable alternative. Finally, once corticosteroid administration is chosen, the possibility

Table 1. Suggested tapering rate for prednisone dosage as a function of the original dose given.

<table>
<thead>
<tr>
<th>Daily dose of prednisone (mg)</th>
<th>Tapering</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>10 mg every 1-2 weeks</td>
</tr>
<tr>
<td>25-50</td>
<td>5-10 mg every 1-2 weeks</td>
</tr>
<tr>
<td>15-25</td>
<td>2.5 mg every 2-4 weeks</td>
</tr>
<tr>
<td>&lt;15</td>
<td>1.25-2.5 mg every 2-6 weeks</td>
</tr>
</tbody>
</table>

Table 1. Suggested tapering rate for prednisone dosage as a function of the original dose given.
of pharmaceutical protection against osteoporosis should be taken into consideration.3

Other immunosuppressive drugs

The 2004 guidelines recommend the addition of azathioprine, 75-100 mg (or 2-3 mg/kg/day) or cyclophosphamide in cases refractory to corticosteroids. However, in this case, too, the recommendation comes from a limited number of cases, namely 5 cases for azathioprine and just 1 case (!) for cyclophosphamide.35 There are also scanty data concerning the administration of methotrexate and cyclosporine.35 In addition, a recent publication reported control of recurrence in 3 paediatric patients with refractory recurrent pericarditis using the interleukin-1b antagonist anakinra.36

To conclude, data regarding the administration of immunosuppressive agents are still insufficient. Their administration should be reserved for rare, particularly refractory cases. The cheapest and least toxic drugs, such as azathioprine and methotrexate, should be preferred, and always with the patient’s consent.35

Drug combinations

It can be gathered from the discussion above that the treatment of IRP, especially in its resistant forms with hard-to-control pain and frequent relapses, should include a combination of drugs.3,10 Figure 1 shows a proposed algorithm for the treatment of IRP, based on current knowledge drawn from evidence-based medicine.

The combination should include 2 or 3 drugs, and specifically an NSAID in recommended doses, colchicine and, more rarely, if judged essential, a corticosteroid, probably in a low-dose regimen with dose tapering.11 Resorting to immunosuppressive drugs is reserved for the most refractory cases, even though there

Figure 1. Proposed therapeutic algorithm in cases with idiopathic recurrent pericarditis using an evidence-based approach. NSAID – non-steroidal anti-inflammatory drug.
is insufficient documentation of their efficacy, at least at present.\textsuperscript{11} Also, during the course of therapy, the patients’ compliance with medical instructions should be monitored. Patience on the part of the treating physician and patient, in combination with the appropriate medical therapy appear to be both essential for the successful treatment of the disease.\textsuperscript{11}

**Prognosis in IRP**

It needs to be emphasised that the only parameter that has been associated with an increased risk of recurrence after an acute episode of idiopathic pericarditis is the administration of corticosteroids.\textsuperscript{5} Corticosteroids probably increase the incidence of recurrence via an increase in the viral antigen load (causing an increase in viral proliferation with a parallel reduction in clearance of the virus).\textsuperscript{2,5}

As regards IRP itself, despite its negative effect on the patients’ quality of life, the long-term prognosis is good.\textsuperscript{3,9,40} A recent meta-analysis examined 8 clinical series that included a total of 230 patients with IRP.\textsuperscript{40} During a mean follow-up period of 61 months, cardiac tamponade was recorded in 3.5% of cases, while there were no cases of constrictive pericarditis or left ventricular dysfunction. Isolated episodes of atrial fibrillation that were observed during recurrences were without clinical significance. In another review of the main clinical series of IRP the incidence of tamponade was 1.7% and of constrictive pericarditis 0.4% (even lower than that of acute idiopathic pericarditis, which is ~ 1%).\textsuperscript{11}

It is accordingly concluded that the long-term outcome of IRP is good, and the patients should be reassured about the benign nature of their disease.

**Conclusions**

IRP, a mysterious disorder until the recent past, is nowadays becoming better understood with regard to its pathogenetic mechanisms and therapeutic management. Clinical investigation, with the contribution of technology, and molecular biology in particular, are the strands of Aphrodite’s thread, which can lead us out of the labyrinth to a full understanding and control of the disease.

The need to draw up new guidelines that will embody the latest data concerning the proper treatment of pericardial diseases, including IRP, is compelling.

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