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REVIEW ARTICLE

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Complement blockade in the management of antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are characterized by the presence of ANCA, particularly those directed against proteinase 3 (PR3) or myeloperoxidase (MPO). At present, the most accepted pathogenic pathway is based on the pathogenic nature of ANCA, which stimulate neutrophils with the consequent activation of the alternative complement pathway, leading to the production of C5a, an anaphylatoxin which plays a key role in amplifying the inflammatory process in AAV. Remission induction in patients with AAV continues to depend on the use of glucocorticoids (GC) in combination with rituximab or cyclophosphamide. Indeed, there are very limited treatment options and a clear need for strategies that reduce the use of GC without compromising efficacy. Avacopan is the first drug specifically developed for patients with AAV as its mechanism of action inhibits C5aR1, thus acting on one of the pathophysiological mechanisms of AAV.

Keywords: Complement. Antineutrophil cytoplasmic antibodies-associated vasculitis. Avacopan.

Introduction

AAV are characterized by the presence of antineutrophil cytoplasmic antibodies (ANCA), the most common of which are those that directed against proteinase 3 (PR3) or myeloperoxidase (MPO)3. At present, the most accepted pathogenic pathway is based on the pathogenic nature of ANCA, which stimulate neutrophils with the consequent activation of the alternative complement pathway and production of C5a, an anaphylatoxin which plays a key role in amplifying the inflammatory process in AAV. C5a, through its binding to the C5aR1 receptor, attracts, and activates more neutrophils and increases vascular permeability, thus contributing to the injury produced in the blood vessel (Fig. 1)4,5.

In Spain, the estimated incidence of GPA is 2.1-2.9 cases per million residents/year, the incidence of...
Figure 1. Diagram representing the pathogenesis of vascular lesions in ANCA-associated vasculitis. The events indicated from the left to right occur sequentially in each injury site and start in multiple sites until remission induction. Neutrophil priming — for example, through cytokines generated by an infection — entails exposure to ANCA antigens on the neutrophils’ surface and microenvironment. ANCA contribute to neutrophil activation, which adhere to the endothelium and penetrate the vessel walls, in addition releasing destructive inflammatory mediators. ANCA-activated neutrophils also produce factors that activate the alternative complement pathway, which results in the generation of C5a which, through its binding to the C5aR1 receptor, amplify the inflammation, attracting and activating more neutrophils. Avacopan (CCX168), C5aR1 antagonist (NCT02994927, NCT01363388, NCT02222155), and Vilobelimab (IFX-1), anti-C5a antibody (NCT03895801, NCT03712345) are complement-blocking therapies with trials in patients with GPA or MPA. In vessel wall rupture sites, the plasma spills into the necrotic area and coagulation factors are activated to produce fibrin, leading to fibrinoid necrosis in the tissue vessels and glomerular crescents. Leukocytoclasia is also produced as a consequence of leukocytic apoptosis or necrosis and due to neutrophil NETosis. In few days, infiltration of macrophages and lymphocytes occurs, starting the scarring process through the deposit of collagen from activated fibroblasts and myofibroblasts (only the activation of monocytes by ANCA is shown on the right side, but this occurs in parallel with neutrophil activation in all acute injury sites). NET: neutrophil extracellular trap.

Adapted from Jennette et al.5

MPA is 3.4–7.9 cases per million residents/year, and the estimated prevalence of AAV is 44.8 cases per million residents and has been increasing in recent decades6,7. Given that its prevalence is < 50 cases/100,000 residents, AAV are considered a rare disease8.

Treatment of AAV

At present, there are few treatment options for patients with severe GPA or MPA. The recommendation is to use rituximab (RTX), cyclophosphamide (CYC), or the combination of both together with glucocorticoids (GC) to
induce disease remission. In regard to the use of oral GC, it is recommended to start treatment with a high dose of oral prednisone (50-75 mg/day) during the 1st week and continue with a rapid dose reduction regimen. In addition, intravenous pulses of methylprednisolone (dose of 1-3 g) are commonly used. There are various factors to take into account in the choice of immunosuppressive treatment. For example, RTX is recommended as the preferred option in patients in relapse whereas in patients with severe renal involvement (serum creatinine > 300 μmol/L), the preferred option is CFM or combination therapy of CFM with RTX; plasmapheresis in addition to the immunosuppressive treatment can be considered in these patients.

Once disease remission is achieved, it is recommended to continue with immunosuppressive treatment to prevent relapses. The most recent recommendations propose the use of RTX as the treatment of choice in maintaining remission. Alternatives to consider include azathioprine (AZA), methotrexate (MTX), and mycophenolate mofetil (MMF). The use of low-dose GC is also considered, but the evidence is limited and its recommendation varies according to factors such as the concomitant immunosuppression or the type of ANCA. The duration of maintenance therapy is not well-defined, though the recommendation is between 18 months and 4 years, depending on factors such as risk of relapse, ANCA-PR3 positivity, the patient’s preferences, and the risk of maintaining the immunosuppression.

Relevant clinical problems in patients with AAV

In recent decades, advances in diagnostic techniques, greater knowledge of the disease, and the introduction and optimization of immunosuppressive treatment regimens have improved the prognosis of AAV. The mortality rate at 1 year was reduced 80% in untreated patients to 11% after the introduction of treatment with GC and CFM. In consequence, AAV have become chronic diseases with frequent relapses; it is estimated that 30-50% of patients will have a relapse of their disease in a 5-year period.

Despite the aforementioned advances, mortality among patients with AAV remains 2.6 times higher than in the general population, mainly due to complications of the disease, such as renal failure or pulmonary hemorrhage, and complications of the immunosuppressive treatment such as infections, which cause up to 50% of deaths during the 1st year. The cumulative GC dose in these patients, in whom prolonged use is frequent, directly contributes to the onset of common complications such as infections, cardiovascular disease (CVD), diabetes, hypertension, and osteoporosis. Therefore, there is a need to identify new treatment approaches that contribute to minimizing the use of GC without any additional risk.

One of the main objectives in AAV is to minimize the irreversible organ damage that occurs in these patients, especially in the kidney. It has been demonstrated that renal, ENT, and treatment-related damage (CVD, diabetes, osteoporosis, and cancer) increases with time. Indeed, it is estimated that one out of every three patients with AAV has severe organ damage (VDI ≥ 5) at 7 years of follow-up. Of note among the factors that contribute to increasing organ damage are the disease’s severity at diagnosis, age, the number of relapses, and prolonged use of GC. Therefore, strategies that facilitate an early diagnosis or faster disease control, that reduce the relapse rate, and that allow for decreasing the use of GC could be decisive for mitigating organ damage in patients with AAV. Likewise, the identification of early biomarkers of activity could be key for evaluating treatment response or the early identification of relapses, thus contributing to a more rational, individualized use of immunosuppression.

Avacopan in AAV

Avacopan selectively and competitively interferes with the binding of C5a to the C5aR1 receptor, thus reducing chemotaxis and neutrophil activation and, with this, the characteristic inflammatory process of AAV. Two Phase II clinical studies with avacopan have been conducted in patients with AAV: CLEAR and CLASSIC.
The CLEAR study evaluated the efficacy and potential GC-sparing effect of avacopan, comparing the following treatment groups: (1) prednisone (60 mg/day at the start; \( n = 20 \)), (2) avacopan (30 mg twice/day) with a reduced dose of prednisone (20 mg/day at the start; \( n = 22 \)), and (3) avacopan without prednisone (\( n = 21 \)). All patients also received immunosuppressive treatment with CFM or RTX. Avacopan demonstrated non-inferiority in the response rate at 12 weeks (70% prednisone, 86.4% avacopan with prednisone, 81% avacopan without prednisone) with a similar safety profile in terms of adverse events (AE) reported (91% prednisone, 86% avacopan with prednisone, and 96% avacopan with prednisone)\(^24\).

The CLASSIC study evaluated the safety and possible efficacy of two doses of avacopan, 10 mg (\( n = 13 \)) or 30 mg (\( n = 16 \)) twice/day compared to a placebo (\( n = 13 \)), in addition to standard treatment (CFM or RTX + GC, 60 mg/day at the start with a gradual 20-week dose reduction regimen). No differences were observed between the groups in regard to safety, with severe AE reported in 15% of patients treated with the placebo and 17% in the combination of the two groups treated with avacopan. In addition, avacopan 30 mg was numerically superior in some secondary outcome measures, such as early remission, recuperation of the estimated glomerular filtration rate (eGFR), and lifestyle evaluations\(^25\).

The pivotal phase III ADVOCATE clinical trial\(^26\) is a multicenter, double-blind, randomized, placebo-controlled study that included 331 patients with active and severe AAV (GPA or MPA). Patients were randomized into receiving avacopan (30 mg twice/day) for 52 weeks or an oral prednisone regimen (60 mg/day at the start with a 21-week dose reduction regimen). All patients also received RTX or CFM followed by AZA. Avacopan demonstrated non-inferiority in remission induction at 26 weeks (72.3% avacopan vs. 70.1% prednisone; \( p < 0.001 \) for non-inferiority) and superiority in maintaining remission at 52 weeks (65.7% avacopan vs. 54.9% prednisone; \( p = 0.007 \) for superiority). In addition, significant differences were observed in several relevant secondary outcome measures such as: (i) Greater recuperation of eGFR, mainly in patients in stage 4 chronic kidney disease at the start (eGFR < 30 mL/min) with a difference between groups of 5.6 mL/min/1.73 m\(^2\) at 52 weeks (95% CI 1.7-9.5), (ii) lower GC toxicity index and fewer GC-related AE (66.3% avacopan vs. 80.5% prednisone), and (iii) improvements in health-related quality of life.

It should be noted that a lower relapse rate was also observed in patients who received treatment with avacopan (10.1% avacopan vs. 21.0% prednisone; HR 0.46; \( p < 0.01 \)). The frequency of severe AE was similar in both groups (40.2% avacopan vs. 45.1% prednisone), although the number of events was lower in patients who received avacopan (116 vs. 166). Severe infections were reported in 13.3% of patients who received avacopan and 15.2% of those treated with prednisone while opportunistic infections were reported in 3.6% and 6.7%, respectively. No infections by encapsulated organisms such as Neisseria meningitidis were observed, which had been reported with complement C5 blockers\(^27\). In patients treated with avacopan, elevations in liver enzyme levels were observed more often (5.4% avacopan vs. 3.7% prednisone), which resolved after the discontinuation of avacopan and other hepatotoxic drugs such as cotrimoxazole\(^26\).

Based on these results, the European Medicines Agency (EMA) authorized avacopan in combination with an RTX or CFM regimen for the treatment of adult patients with severe, active GPA or MPA on January 11, 2022.

Conclusions

Remission induction in patients with AAV continues to depend on the use of GC in combination with RTX or CFM. There are few treatment options in these patients and a clear need for strategies that allow for reducing the use of GC without compromising efficacy.

Avacopan is the first drug specifically developed for patients with AAV due to its mechanism of action targeted at C5aR1 inhibition, thus acting on one of the pathophysiological mechanisms of AAV. It is also the first treatment alternative to GC for this disease, achieving better efficacy outcomes in terms of remission maintenance and improvement in some renal parameters. In fact, the outcomes of the CLEAR, CLASSIC, and ADVOCATE studies suggest that complement blockade may favor a greater degree of renal recovery than the few treatment options available at present and with a favorable safety profile for avacopan.

Studies with longer follow-up periods are needed to evaluate the safety of treatment with avacopan over a longer period of time as well as possible interactions with other drugs, especially those that are hepatotoxic.

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**Conflicts of interest**

The authors declare that they have no conflicts of interest.

**Ethical disclosures**

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

**References**

Diagnosis delay, phenotypic variety, and therapeutic outcome of Erdheim-Chester disease

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Abstract

Erdheim-Chester disease (ECD) is a non-Langerhans histiocytic that typically affects middle-aged adults between the fifth and seventh decades of life. It is characterized by systemic xanthogranulomatous infiltration by histiocytes CD68+/CD1a–. In this paper, we collect the main clinical characteristics of eleven patients, diagnosed with ECD at the Virgen del Rocio Hospital in Seville. After first medical contact, it has been possible to reduce the misdiagnoses and this has shortened the time to diagnosis and initiation of treatment, which has resulted in fewer complications.

Keywords: Erdheim-Chester disease. Non-langerhans histiocytosis. Bone tumor. Rare disease.

Introduction

Erdheim Chester disease is a rare pathology, and it is one of the systemic histiocytosis, classified as a non-Langerhans cells histiocytosis. It is a multisystemic involvement with high morbidity due to infiltration with foamy histiocytic cells in the form of xanthogranulomas that are distributed throughout the body. The most frequent involvement occurs at the osteoarticular level, with osteosclerosing lesions predominantly at the metaphysis and diaphyses of long bones¹. The etiology of the disease is unknown and is associated with an intense immune response mediated by Th1 lymphocytes, as well as the mutation of the V600E BRAF gene².³. The definitive diagnosis is established by the appearance of CD68+/CD1a– histiocytes in the tissue biopsy¹. In its absence, the presence of the BRAF V600E mutation or MAPK pathway modification has become the gold standard¹².

Materials and methods

The present study describes the form of presentation, main clinical manifestations, as well as the diagnostic and therapeutic methods used in ECD, through a series of 11 patients collected at the Rare Disease Unit at Virgen del Rocio University Hospital in Seville, at third level hospital in Spain.

We performed an intelligent search in our patient database from the year 2000 to the present, including in the search: non-Langerhans cells and Erdheim-Chester disease.
We have omitted the personal data of the patients and their identification in the images. Informed consent has been requested for the conduct of this study. The Helsinki WMA guidelines were followed.

Results

Onset characteristics of the patients

We have obtained information from 11 patients (six men and five women) with a median age of onset and diagnosis of 41 years and 44 years, respectively, with a mean diagnostic delay of 3 years.

The most characteristic onset in our series of patients is a presentation with general symptoms such as constitutional symptoms with arthralgias, fever, and lymphadenopathy. In only two cases, the debut was considered severe, as it included cardiovascular involvement (periaortitis and heart failure). A summary of the patient's characteristics is given in Table 1.

Clinical features

In our patients, bone involvement was the most frequently found after diagnostic positron emission tomography-computed tomography (PET-CT) (nine of the 11 patients).

In terms of frequency, the most common involvement after bone disease was nephrourological and endocrine, with the appearance of typical disease manifestations such as hairy kidneys, retroperitoneal fibrosis, and diabetes insipidus.

The most severe involvement was cardiovascular manifestations; four patients presented the classic periaortict fibrosis (Fig. 1). In one patient, pericardial effusion was detected, and he even suffered cardiorespiratory arrest with an etiology not fully identified, which was attributed to sudden cardiac rhythm disturbances (during his admission to the intensive care unit (ICU), the patient had several episodes of bradycardia and supraventricular tachycardia).

A summary of the patient's clinical manifestations is given in Table 2.

Diagnosis and its difficulties

It has already been mentioned that ECD is an entity with very diverse clinical manifestations and that a high clinical suspicion is required for its diagnosis. In our series of patients, the diagnostic delay in the very first patients diagnosed in our unit (patients 1-4) was about 7.5 years; however, in the last patients (4-11), the diagnostic delay has decreased, and it is frequent that ECD is among the clinical judgments to be discarded in the first visits. At present, the average delay is < 2.5 years.

The most frequent misdiagnosis at debut includes metastasis of non-infiltrative primary tumor, idiopathic retroperitoneal fibrosis, eosinophilic granuloma, and lymphoma. In most of the patients, the appearance of key images on PET-CT simplified the differential diagnosis. In three of the patients, the diagnosis was reached after histopathological and immunohistochemical reinterpretation of biopsy specimens.

Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Onset</th>
<th>Diagnosis</th>
<th>Exitus</th>
</tr>
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<td>Male</td>
<td>34 year</td>
<td>43 years</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>58 year</td>
<td>66 years</td>
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</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>39 year</td>
<td>41 years</td>
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</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>20 year</td>
<td>27 years</td>
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</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>50 year</td>
<td>51 years</td>
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</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>23 year</td>
<td>23 years</td>
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</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>49 year</td>
<td>49 years</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>36 year</td>
<td>36 years</td>
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</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>50 year</td>
<td>52 years</td>
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</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>64 year</td>
<td>64 years</td>
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</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>27 year</td>
<td>29 years</td>
<td>No</td>
</tr>
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</table>

Figure 1. Inflammatory cuff suggestive of periaortitis.
Table 2. Organ involvement and clinical features

<table>
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<tr>
<th>Patient</th>
<th>Cardiovascular</th>
<th>Neurologic</th>
<th>Pulmonary</th>
<th>Bone</th>
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<th>Endocrine</th>
<th>Ophthalmic</th>
<th>Dermatologic</th>
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<td>Piramidalism, Cerebral tumors</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Periaortitis</td>
<td>Frontal cerebral tumor Parcial seizures</td>
<td>No</td>
<td>Yes</td>
<td>Hairy kidneys</td>
<td>Diabetes insipidus Hypogonadotropic hypogonadism</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>Condensative infiltrates</td>
<td>Yes</td>
<td>Obstructive uropathy</td>
<td>Diabetes insipidus</td>
<td>No</td>
<td>Lichen pigmentosum</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Periaortitis Pericardic effusion Sinusal bradycardia and cardiac arrest Supraventricular tachycardia</td>
<td>Seizures</td>
<td>No</td>
<td>Yes</td>
<td>Myositis ossificans</td>
<td>Obstructive uropathy Hairy kidney</td>
<td>Diabetes insipidus Hypogonadotropic hypogonadism</td>
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</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Obstructive uropathy Hairy kidney</td>
<td>Hypogonadotropic hypogonadism</td>
<td>No</td>
<td>No</td>
<td></td>
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<td>No</td>
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<td>7</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Autoimmune hypothyroidism</td>
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<td>Micronodular infiltrate</td>
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<td>Diabetes insipidus</td>
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<td></td>
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<tr>
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<td>Sinusal bradycardia</td>
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<td>No</td>
<td>Diabetes insipidus</td>
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<td>No</td>
<td></td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>Primary hypothyroidism</td>
<td>No</td>
<td>No</td>
<td></td>
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<tr>
<td>11</td>
<td>Periaortitis and coronary stenosis</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

The rest of the patients were diagnosed with a suspicion oriented toward the symptoms once the sample was taken. The biopsies obtained from the lesions were: brain by surgical excision figure 2, renal capsule of Gerota and retroperitoneal fibrous tissue by intraoperative biopsy, skin biopsy by punch, bone biopsies, bone marrow, or lymphatic biopsies.

In one patient, histological samples were not obtained due to the patient’s own refusal; the diagnosis in this patient was made based on the clinical manifestations present (periaortitis and retroperitoneal fibrosis) and the PET-CT images (epicardial tissue infiltration involving proximal areas of the coronary arteries, axillary hypercaptant lesions suspicious for adenopathy). Other pathologies such as IgG4 disease and chronic Kawasaki lesions were ruled out.

In those patients with histopathological samples, BRAF V600 gene analysis was performed to determine, whether they were candidates for third-line specific immunotherapy in the event of failure of interferon and MEK inhibitors (cobimetinib). In the sample of patients, four of them were positive for the BRAF V600 gene mutation, five were negative, in one, there was not enough histological sample, and in another patient, a biopsy was not performed by choice.

Treatment and clinical course

Once the diagnosis was oriented or concluded, the treatment was started. All patients received glucocorticoids in addition to the basic treatment.
The most commonly used dose of glucocorticoids comprised between 60 and 40 mg of prednisone per day. On some occasions if the general clinical condition worsened, methylprednisolone pulses were used at doses between 0.5 and 1 mg/kg on three consecutive days with good response. The most used treatment regimens are those including pegylated interferon 130.000-180.000 ug (some patients started treatment with interfering alpha 2b with poor tolerance). In addition to this treatment, immunomodulators such as Anakinra (used in four of the patients) and Cobimetinib (in another four patients) were used as second line treatment.

For the control and follow-up of the disease, PET-CT was used in eight of the patients on an annual basis or when there was suspicion of disease progression to decide on the continuation or change of treatment. PET-CT showed in these patients a partial metabolic response in soft tissues and a greater response at bone level, although disease activity persisted.

It is worth to notice the great improvement with complete disappearance of the skin lesions in a short time and with almost complete response in one of the patients when starting interferon.

In our registry, three of the patients died. The first patient with brain involvement was admitted to our department for respiratory failure, and a new PET-CT scan showed progression of brain lesions. The patient was dead due to respiratory insufficiency of infectious etiology.

The second patient was suspended from treatment due to poor tolerance, worsening of performance status index (PS), and progression of the disease to the central nervous system (CNS) and dead during a palliative care admission due to status epilepticus.

The tenth patient developed a recurrent pleural effusion, in which the study was diagnosed as

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pathology</th>
<th>BRAF V600E</th>
<th>General symptoms</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Cerebral biopsy</td>
<td>Positive</td>
<td>No</td>
<td>Alfa interferon + Pegylate interferon + prednisone</td>
</tr>
<tr>
<td>2</td>
<td>Kidney and retroperitoneum biopsy</td>
<td>Positive</td>
<td>Fever Retroperitoneum fibrosis</td>
<td>Pegylate interferon + prednisone</td>
</tr>
<tr>
<td>3</td>
<td>Skin biopsy</td>
<td>Negative</td>
<td>Retroperitoneum fibrosis</td>
<td>Pegylate interferon + cobimetinib</td>
</tr>
<tr>
<td>4</td>
<td>Kidney biopsy</td>
<td>Positive</td>
<td>Retroperitoneum fibrosis</td>
<td>Pegylate interferon + prednisone + Anakinra</td>
</tr>
<tr>
<td>5</td>
<td>Adenopathy biopsy</td>
<td>Positive</td>
<td>Retroperitoneum fibrosis Fever</td>
<td>Alfa interferon + Pegylate interferon + cobimetinib</td>
</tr>
<tr>
<td>6</td>
<td>Bone biopsy</td>
<td>Negative</td>
<td>Retroperitoneum fibrosis</td>
<td>No treatment</td>
</tr>
<tr>
<td>7</td>
<td>Bone/retroperitoneum biopsy</td>
<td>No performed</td>
<td>No</td>
<td>Anakinra</td>
</tr>
<tr>
<td>8</td>
<td>Bone biopsy</td>
<td>Negative</td>
<td>Retroperitoneum fibrosis</td>
<td>Pegylate interferon</td>
</tr>
<tr>
<td>9</td>
<td>Bone biopsy</td>
<td>Negative</td>
<td>No</td>
<td>Pegylate interferon + Anakinra + vinblastine + cobimetinib</td>
</tr>
<tr>
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<td>Adenopathy biopsy</td>
<td>Negative</td>
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<tr>
<td>11</td>
<td>No performed</td>
<td>No performed</td>
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</table>
Discussion

As we have seen, ECD presents a multitude of different clinical presentations. Whether in pediatric age or in the elderly, the number of manifestations of the disease requires a great deal of knowledge on the part of the clinician and a high degree of suspicion in order to reach a diagnosis. With an incidence between the fifth and seventh decades of life, patients present cardiac, endocrine, pulmonary, neurological, and bone involvement, which requires a differential diagnosis between pathologies such as lymphoma, osteoblastic metastases, sarcoidosis, or metabolic disorders such as Gaucher disease or Niemann-Pick.

Bone involvement revealed by bone scintigraphy was present in all but one patient, with diaphyseometaephysseal involvement typical of the disease being present in nine of them. In a review of the disease, several bone involvement is found in 96% of the patients, although pain is only manifested in about half of them (in the case of our patients only two). We must be cautious, since, although it is one of the most frequent conditions of the entity described in the study, there are patients who do not present it. Therefore, its absence should not make us ignore the possibility of being before a ECD as already mentioned by Iborra et al. in a study of 12 clinical cases, where there were patients who did not present bone involvement.

Approximately 75% of patients suffer cardiovascular involvement, conferring a worse prognosis to the disease, being the cause of death in 60% of patients.

Morbidity and mortality depend on the extent and severity of cardiac involvement and magnetic resonance imaging is a very useful test in the diagnosis of cardiac affection. The ascending and descending aorta are the most frequently affected with fibrosis, also is described cases of stenosis of the renal and cerebral arteries, often requiring a differential diagnosis between Takayasu’s arteritis. Nevertheless, these clinical characteristics are rare presentations with high mortality and their management should be considered in future research, since the etiopathogenesis is different from that of atherothrombotic coronary artery disease.

In the study Arnaud et al., they documented neurological involvement of the disease in 51% of patients, being the direct cause of all deaths in 29%, as well as an independent factor of poor prognosis. The manifestations are multiple, from exophthalmos to cerebellar ataxia, pyramidal syndrome, etc., depending on the sites affected by the disease. Lumbar puncture is not recommended since there is no presence of histiocytic cells in cerebrospinal fluid. Magnetic resource imaging (MRI) is the best test to evaluate central nervous system (CNS) involvement.

Another frequent location of the disease is the infiltration of the retroperitoneal space. Present in up to 68% of patients, it gives rise to fibrosis that can involve both kidneys causing the appearance of the characteristic image of “hairy kidneys” (Fig. 3), while it can cause bilateral obstruction at the ureteral level with hydronephrosis and renal failure. One of the most useful tests to demonstrate retroperitoneal involvement and at the same time the involvement of the great thoracic and abdominal vessels is CT.

PET-CT is the test proposed for patient follow-up since it is the only one that provides a global vision of the possible affectations that ECD may be causing in the organism. In all our patients, a PET-CT scan was performed which showed both metabolic response with treatment and the appearance of new foci of disease or progression in three of the patients. In patients who in the first instance do not show bone involvement, Arnaud et al. and Goyal et al. propose whole body MRI as an alternative test for the follow-up of patients, due to the absence of irradiation of the organism and a good sensitivity to recognize cardiac or visceral involvement of the test.

The pathogenesis underlying the treatment of the disease is still unknown. Through the study of the
BRAF mutation, it has been demonstrated that Langerhans histiocytosis and ECD have a common pathogenic basis, evidenced by the premise that this mutation is only found in these two types of histiocytosis, not being present in other forms such as Rosai-Dorfman disease, histiocytic sarcoma, or interdigitating dendritic cell sarcoma. It is this BRAF V600E mutation that opens the door to new therapeutic possibilities. Present in up to 54% of patients, this mutation not only supports diagnosis, but is also a new window and target for trials of new treatments.

Until now, ECD has been treated using glucocorticoids, with a limited impact on the disease, and interferon alpha the one that demonstrates regression of clinical manifestations and an increase in survival in different analyses and studies. The response to interferon and other treatments corroborates an underlying immune-based alteration that has yet to be adequately investigate. Other immunosuppressants used with less success are cladribine, imatininb, or sumatinib. Bisphosphonates have been used to try to palliate bone resorption and among the new treatments, the interleukin-1 inhibitor (Anakinra) has shown improvement of disease symptoms at doses similar to those of patients with rheumatoid arthritis and without setting an exact time limit for treatment.

Nevertheless, it is the mentioned BRAF mutation that offers us a new drug, vemurafenib, which promises to be an inescapable drug in the treatment of ECD. Based on the premise of increased survival of melanoma patients, Haroche et al. present a new study of three patients with ECD treated with vemurafenib at an initial dose of 1920 mg/day. They demonstrate a dramatic and rapid efficacy of treatment in all three patients, with regression of perivascular and cardiac lesions, as well as skin, visceral, bone, or cranial lesions among others and a more rapid decline in acute phase reactants with respect to interferon alpha, all documented by follow-up with PET-CT and computed tomography.

Due to the expansion of the use of MEK inhibitors in the treatment of ECD with progression, in our service, we have started to perform genetic studies of biopsies taken positive for non-LCH of NRAS, PID3CA, or RAS-PI3K-AKT expression.

Conclusion

The incidence of ECD has increased during the last decade. Despite its great clinical variety, the study of the most frequent organic manifestations, as well as a greater knowledge on the part of clinicians of this entity, corroborates this finding. Undoubtedly, ECD is a diagnostic challenge for the physician who must keep in mind the existence of this pathology to be able to make the diagnosis. A high diagnostic suspicion is vital given the heterogeneity that characterizes the disease. Patients with less diagnostic delay and, therefore, early initiation of targeted therapy, severe complications of the disease have not developed or have decreased in their expressivity, improving the patient's prognosis.

The light shed by new studies on its etiopathogenesis is allowing the discovery of promising targets for treatment and patient survival. Even so, the low incidence of the disease and the widespread ignorance that still persists makes it difficult to carry out adequate clinical trials, which are necessary for a more reliable and in-depth study.

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Author-level metrics: $h$-index and beyond

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Abstract

Author-level metrics are usually employed for academic promotion and research funding. The $h$-index is a way of measuring scientists’ productivity and impact on their field, determined by the number of publications and the number of times those publications have been cited. However, the $h$-index calculation does not capture the influence of factors such as research topics, article types, highly cited items, self-citations, number and position of authors, and academic career length. Nonetheless, variants of $h$-index that address some of these limitations correlate widely with their original metric, are not available in bibliographic databases and, overall, add little for measuring research productivity.

Keywords: Authorship. Hirsch index. Bibliometrics. Internal medicine.

Introduction

Assessing academic productivity of clinical researchers is an evolving issue with the search for the ideal index still going on. The $h$-index is considered the mainstream author-level metric due to its simple calculation, but it has also received criticisms. In fact, assessment of individual researchers should consider a broad range of bibliometric measures, not only a single indicator. Definition of $h$-index, its strengths and weaknesses, as well as variants and alternatives to this standard bibliometric indicator will be addressed. This article is intended to be a concise introduction to the author-level metrics that evaluate scholarly works.

Total publications and citations

The total number of publications reflects the author’s productivity and can be obtained by sourcing information from databases, such as Web of Science (WoS), Scopus, or MEDLINE. Unfortunately, neither the type of articles (original, review, editorial, research letter, letter to the Editor, case report, etc.) nor their quality are taken into consideration by this metric. Therefore, many low-quality items (e.g., letters and case reports) can boost publication record numbers.

On the other hand, the total number of citations, also available at WoS and Scopus, is a simple measure of the impact of research that reflects the interest in the cited items. However, the number of citations is influenced by the specific research topic (i.e., it is easier for a scholar to receive citations if he/she write on a topic on which large number of articles are published) and does not consider the quality of the citing journal. Consequently, these two crude quantitative measures (total number of publications or citations) are not generally used in academia and or in the evaluation of research policy results.

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The *h*-index is preferable to metrics that measure only a researcher’s number of publications or citations received by these publications. It was created in 2005 by Jorge Eduardo Hirsch, an Argentine-American professor of physics at the University of California (San Diego, USA)\(^2\).* The *h*-index is an intersection of productivity (number of papers published) and recognition (number of citations to these papers). It was defined by Hirsch as follows: “A scientist has index *h* if *h* of his or her number of papers \((N_p)\) have at least *h* citations each and the other \((N_p - h)\) papers have \(\leq h\) citations each”\(^3\). That is, *h* equals the number of papers that have received at least *h* citations (Fig. 1). Hence, if a scientist has currently an *h*-index of 60 (for example, its inventor Dr Hirsch), then that means he/she has 60 papers with at least 60 citations each. Both productivity and impact are required for a high *h*-index; neither a few highly cited papers nor a long list of papers with only a handful of (or no) citations will yield a high *h*-index. Hirsch’s original work from 2005 has been cited 6126 times according to WoS (accessed July 31, 2022) and 6508 times according to the Scopus database (accessed July 31, 2022).

The *h*-index can be obtained through databases such as WoS, Scopus, and Google Scholar. Overall, Google Scholar returns significantly higher *h*-index scores than Scopus or WoS; the latter being the most stringent. The underlying reason is that these databases have varying coverage of publications and citations\(^3\).

What is a good *h*-index is a matter of opinion. In general, an *h*-index of 20 characterizes a successful scientist, 40 an outstanding scientist, and 60 or more a truly exceptional one. However, this is a broad generalization and actual figures may vary enormously among different disciplines or fields and are influenced by the length of a research career. The median *h*-index of 195 laureates with the Nobel Prize in Physiology and Medicine between 1901 and 2009 was 43 (WoS) at the time of the award\(^4\); yet for 42 laureates from 2001 to 2017, it raised to 72.5\(^5\). This discrepancy may arise from the fact that scientific publications and citations grow steadily over time\(^6\).

In 2021, nine highly cited Spanish researchers in Clinical Medicine were recognized in WoS due to their scientific production over the past decade (*h*-indexes accessed on July 31, 2022): Jesús Fernando San Miguel (Hematologists from Clínica Universitaria de Navarra, *h*-index = 120), Josep Tabernero (Oncologist from Hospital Vall d’Hebron de Barcelona, *h*-index = 114), Jordi Bruix (Hepatologist from Hospital Clinic de Barcelona, *h*-index = 113), José Luis Zamorano (Cardiologist from Hospital Universitario Ramón y Cajal, Madrid, *h*-index = 104), Enriqueta Felip (Oncologist from Hospital Vall d’Hebron de Barcelona, *h*-index = 95), Joaquin Bellmunt (Oncologist from Hospital del Mar, Barcelona; *h*-index = 86), Luis Paz-Ares (Oncologist from Hospital Universitario 12 de Octubre, Madrid, *h*-index = 86), Javier Cortés (Oncologist from International Breast Cancer Center, Barcelona, *h*-index = 80), and Maria Victoria Mateos (Hematologist from Hospital Clínico de Salamanca, *h*-index = 79). Table 1 shows current *h*-indexes of Presidents of the Sociedad Española de Medicina Interna (SEMI) over the past 30 years.

The *h*-index, however, does not capture the full history of a scientist’s contributions and has several caveats\(^6\):

**Figure 1.** Graphical representation of an author’s *h*-index (57).
It does not consider issues of multiauthorship. That is, the author's position in the paper is not considered, so there is no extra credit for being the first (second or last) author, which usually indicates a greater role in the investigation. Similarly, some scientists may achieve a high h-index simply because they co-author papers with other highly productive researchers, but either they occupy a less relevant position in the article or, even worse, they are “guest/gift” authorships (the author is listed solely as a gesture of respect or as an attempt to make a paper appear more credible than it is) or “coercion” authorships (a person in a position of authority uses this authority to compel another author to include him/her on a manuscript). These last two categories of authorship are contemplated as outright unethical practices.

Comparing scientists from different disciplines or even with different research topics within the same discipline is problematic due to disparity in citation counts. For example, a researcher on human immunodeficiency virus (HIV) is more likely to achieve higher h-indexes than a researcher on pleural diseases, because in the past 40 years, 7 times more has been published on the former subject than on the latter. In fact, according to Expertscipe (https://expertscape.com/), the world’s number one and two HIV experts have WoS/Scopus h-indexes (accessed on July 31, 2022) of 91/103 (Kenneth H. Mayer) and 96/95 (Robert Siliciano), whereas h-indexes of the two top ranked experts in pleural diseases are 38/39 (Najib M. Rahman) and 39/41 (José M. Porcel), respectively.

The h-index does not properly credit authors who publish few but highly influential papers. For example, a scientist A with 20 papers cited 20 times each would have an h-index of 20, whereas a scientist B with ten documents which were cited 200 times each would only achieve an h-index of 10. Scientist B publishes fewer documents, but their impact is much higher than those of scientist A. In other words, scientist A publishes twice as many articles as scientist B, although with a much lower impact. Despite this, according to the h-index, scientist A would be regarded as much more successful than scientist B.

The h-index is influenced by the length of a scientist’s career or lifetime citedness, which is disadvantageous to early career researchers that usually won’t have a very high h-index. One rule that is widely accepted is that a respectable h-index score would be at least equal to the number of years that a scientist has put into his or her work.

Self-citation practices may increase the h-index, although some databases (e.g., Scopus) allow calculation of the h-index after removing self-citations.

The h-index cannot decline even if a scientist does not publish any paper after a number of active years of publication. This metric can only increase over time, so it is not able to differentiate between active and inactive researchers. In fact, the h-index score of deceased authors commonly raises giving the false impression of growing productivity.

h-index variants and other metrics

Variants of the h-index try to circumvent the shortcomings of this metric though, in general, they are regarded as superficial enhancements. Several dozen variants of h-index have been proposed, although only some significant ones will be commented on.
Co-authorship normalized metrics

The \( h_m \)-index was proposed by Schreiber in 2008 and is determined in a similar way to the \( h \)-index, but counting the number of papers fractionally based on the number of authors\(^7\). A weight is assigned to each publication as the inverse of the number of authors (e.g., 1 author paper = 1, 2 author paper = 0.5, and 3 author paper 0.33). The \( h_m \)-index would be the effective number of papers that have been cited \( h_m \) or more times. If a researcher only publishes sole author papers, \( h \)-index equals to \( h_m \)-index, but, in all other cases, \( h_m \)-index will be less than \( h \)-index. This alternative metric, however, does not distinguish between different author positions and is not offered by the standard databases (i.e., it must be calculated manually).

Other co-authorship-adjusted metrics are the ‘profit (p)-index’ (which accounts for number of co-authors and the sequence of authors on the paper)\(^8\) and the \( h \)-fac index (which ponders positively the commitment and participation of the first author)\(^9\).

Evaluating highly cited scientists

The \( g \)-index, which was introduced by Leo Egghe, credits authors of highly cited papers\(^10\). To compute this index, the citations are considered in a descending order. The resultant score is the largest number of top “g articles” receiving together at least \( g^2 \) citations. Hence, a \( g \)-index of 10 indicates that the top ten publications of an author have received at least a total of 100 citations (\( 10^2 \)). The \( g \)-index is always higher than the \( h \)-index and is particularly helpful for comparing researchers with identical \( h \)-index. For example, an author with 10 published articles, three of which are cited 60, 30 and 10 times (100 in total), will have a \( g \)-index of 10 and an \( h \)-index of 3. The \( g \)-index can be calculated on the Harzing Publish or Perish website (https://harzing.com/resources/publish-or-perish) using data from Google Scholar or subscription citation databases.

Another complement to the \( h \)-index for evaluating highly cited scientists or for comparing the scientific output of scientists having an identical \( h \)-index is the so-called e-index, but its calculation is complex\(^11\).

Time-adjusted metrics

The \( m \)-quotient corrects the \( h \)-index for career length, thus facilitating comparisons between scientists with different periods of academic activity. It is calculated by dividing a scientist’s \( h \)-index by the number of years that have passed since the first publication, with a score of 1 being very good indeed, 2 being outstanding, and 3 truly exceptional. Thus, in a person with 20 years of research experience, an \( h \)-index of 20 (i.e., \( m \)-quotient = 1) is very good, 40 is great (i.e., \( m \)-quotient = 2), and 60 (i.e., \( m \)-quotient = 3) is remarkable. However, the first publication is not always the start of an active career in a specific field. In a similar way, the \( m \)-quotient overlooks temporal interruptions in an individual career (e.g., breaks in academic publications for parental leave).

Other indexes that take into account time include the contemporary \( h \)-index (considers the age of an article)\(^12\) or the timed \( h \)-index (compares activity at various 5-year time points)\(^13\). Some databases, such as Google Scholar, calculate author's metrics (\( h \)-index) for the past 5 years.

Other metrics

\( i_{10} \)-index

It refers to the number of publications with at least ten citations. This simple and straightforward measure is only used by Google Scholar, but can be easily calculated from data provided by WoS or Scopus. Likewise, other similar indexes could be derived, such as \( i_{15} \), \( i_{20} \), \( i_{25} \), and \( i_{30} \). It can be used to highlight productivity over impact (\( i_{10} \)) or impact over productivity (e.g., \( i_{50} \), \( i_{100} \), and \( i_{200} \)).

Author impact factor

The author impact factor (AIF) is the analogue for authors of what the impact factor is for journals\(^3\). Basically, the AIF is a dynamic index which expresses the current impact of papers published by authors in recent years, and therefore, it may capture trends and variations of the performance of scholars along their careers\(^14\). The AIF of an author \( A \) for a year \( t \) is the average number of citations given by papers published in year \( t \) to papers published by \( A \) in a given time window (e.g., 2-5 years) before year \( t \). Unfortunately, this metric has not been implemented on bibliographic portals. Erroneously, some scientists think the AIF is calculated by summing up the impact factor of each journal in which they have published an article.

Conclusions

The \( h \)-index is the mainstream author-level bibliometric indicator. It combines quantitative (publication counts) and impact (citation counts) data into a single whole number. However, it does not allow to compare
scientists of different seniority or disciplines, nor it does consider the position of the author within the author list. Particularly, researchers working in non-mainstream areas will have lower $h$-values than those working in highly topical areas. Many variants of the $h$-index with interesting and unique attributes have been proposed which attempt to correct some of its limitations. Nevertheless, they have not attracted much attention, primarily due to their complex formula calculations and the lack of availability in common bibliographic sources.

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