L12. Rheumatoid arthritis vasculitis

Rheumatoid arthritis vasculitis (RAV) affects small- and medium-sized vessels of a subset of patients with RA. This vasculitis, which can be necrotizing or leukocytoclastic, mainly involves small vessels, more than medium-sized. Treatment of systemic RAV is poorly codified. Five-year mortality rates were high, 33 to 43% [1–3], depending on the study considered, with marked morbidity. Among secondary vasculitides, RAV is one of the most severe, as it responds poorly to conventional treatments specifically prescribed for RA [4]. In contrast, its control requires prolonged use of immunosuppressants [5]. More recently, biotherapies have been successfully prescribed [6,7].

**Epidemiology and clinical manifestations**

RAV is rare and has been observed less frequently in the recent years (table I). In the Norfolk (UK) area, the annual RAV incidence was 11.6/million inhabitants between 1988 and 1992, and 3.6/million between 1998 and 2002 [8]. In the Olmsted County, Minnesota series, the 10-year cumulative incidence of RAV, but not other extra-RA manifestations, was significantly lower in the 1995 to 2007 cohort (0.6%) than the 1985 to 1994 cohort (3.6%) [9]. More men might be affected than women but the exact sex-ratio varies according to series [10]. In our practice, we have observed fewer RAV cases since the early 2000s and we hypothesize that use of the most recent biological therapies to treat RA might have had an impact on RAV development. RAV mainly occurs in patients whose RA had started several years earlier and was severe with major bone erosions. Smoking, positive rheumatoid factor and anticyclic citrullinated peptide antibodies are frequent features. It may occur in patients treated with immunosuppressants, and sometimes after rapid steroid tapering. It may arise in patients given antitumor necrosis factor-alpha (TNFα), even though this drug has sometimes been used successfully to treat RAV [6]. At the time of vasculitis onset, RA can be more-or-less inactive. Skin manifestations are frequent, characterized by nodules or livedo. Among systemic manifestations, pleuritis, cardiac involvement and ocular symptoms are the most frequent.

**Clinical manifestations**

Skin, nerves and other major organs can be affected by this vasculitis, which can mimic polyarteritis nodosa with multisystemic involvement.

**Skin manifestations**

Digital microinfarcts are frequently seen, usually subungual and visible through the nail, but they also can be periungual and in the digital pulp. They are frequently associated with subcutaneous skin nodules. These microinfarcts are not considered factors of poor vasculitis prognosis, unless they are associated with systemic manifestations. Some patients also have leg arterial ulcers that respond only to the vasculitis treatment. Livedo reticularis, macula, purpura and digital gangrene can occur. The latter is considered of poor prognosis. Pyoderma gangrenosum has also been rarely described [17], as it can be observed in other vasculitides.

**Peripheral neuropathy**

Mononeuritis multiplex is the most prominent form of RAV neuropathy [2,18]. The following nerves are preferentially involved:

- superficial peroneal nerves;
- sural, radial;
- cubital;
- median nerves.

In its late stage, so many nerves can be involved that mononeuritis multiplex can be mistaken for a symmetric process. Sometimes the polyneuropathy is exclusively sensory, which can be vasculitis-related but has also been associated with Sjögren’s syndrome. Muscle vasculitis is often
found in biopsies, but patients do not usually complain of muscle deficit(s).

**Gastrointestinal involvement**
Abdominal pain is common and disappears under treatment. But some patients can develop severe gastrointestinal perforations, ischemic colitis, pancreatitis and mesenteric infarction. Some of those manifestations are life-threatening and their prognosis is poor.

**Ocular manifestations**
For example, episcleritis and scleritis, can also be observed in RAV [19,20]. Episcleritis is benign, but necrotizing scleritis is a severe painful disease that warrants use of immunosuppressants or biotherapies.

**Complementary investigations**
Inflammation is common. Erythrocyte sedimentation rate (ESR) is elevated. Anemia is frequent. ANCA are not found (some patients test positive for pANCA but antinuclear peroxidase and protein-3 Elisa are negative; lactoferrin could be an antigen involved in pANCA-positive patients). Mixed cryoglobulinemia can be detected together with a low C4-complement fraction. HLA specificity is usually DR4. Most patients carry dual DRB1*0401 alleles. Gorman et al.'s [21] meta-analysis of 14 studies showed that RAV patients were carriers of 3 double-allele epitopes: DRB1*0401/*0401, *0401/*0404 and *0101/*0401.

**Management**

**Outcome**
Systemic manifestations of RAV are severe and indicative of poor outcome. Skin manifestations alone usually have a good prognosis. A better therapeutic strategy has improved survival, but in old series, 5-year survival was around 50% [4]. Even though they have not been specifically evaluated for this entity, the prognostic factors included in the Five-Factor Score [22] can be also considered prognostic for RAV.

**Treatment**
Therapy is not codified and should be adapted to the disease severity.

**Corticosteroid**
All patients with systemic disease are prescribed CS for at least 12 months. High doses may be useful initially. The administration of methylprednisolone pulses (usually 7.5–15 mg/kg IV over 60 min, repeated at 24-h intervals for 1–3 days) has become widely used at treatment onset for severe systemic vasculitis, especially when life-threatening organ involvement or the extension phase of mononeuropathy multiplex is present. This regimen acts rapidly and is relatively safe. The pulse methylprednisolone dose is empirical and doses under 1000 mg may be as effective. The oral CS dose is 1 mg/kg/day of prednisone or its equivalent of methylprednisolone. As the patient’s clinical status improves and the biological markers of inflammation (C-reactive protein, ESR) return to normal, usually within 3 weeks to 1 month, tapering of the prednisone dose can begin.

**Cyclophosphamide**
CYC is, in our clinical practice, prescribed at the dose of 600 to 700 mg/m², given as pulses on days 0, 14 and 28, then every 3 weeks. Oral CYC at the dose of 2 mg/kg/day for 3 to 6 months can also be used, in combination with CS. Side effects have been extensively described and are not disease-specific. Major adverse events associated with CYC administration include hemorrhagic cystitis, bladder cancer (less frequent when pulses are used [23]), bone-marrow suppression, ovarian failure and hematological malignancies. Severe infections represent a major cause of mortality of patients with systemic necrotizing vasculitides, especially while they are receiving high CS doses with adjunctive immunosuppressive drugs.

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**Table I**

**Epidemiology of rheumatoid arthritis (RA) vasculitis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study population, country</th>
<th>Prevalence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watts et al., 2004 [8]</td>
<td>General, UK</td>
<td>–</td>
<td>3.6/million</td>
</tr>
<tr>
<td>Mongan et al., 1969 [13]</td>
<td>Hospitalized, USA</td>
<td>8 p. 100</td>
<td>–</td>
</tr>
<tr>
<td>Panush et al., 1983 [14]</td>
<td>Not selected, USA</td>
<td>&lt; 1 p. 100</td>
<td>–</td>
</tr>
<tr>
<td>Turesson et al., 1999 [15]</td>
<td>Not selected, Sweden</td>
<td>7.9 p. 100</td>
<td>2.92/100</td>
</tr>
<tr>
<td>Carmona et al., 2003 [16]</td>
<td>Not selected, Spain</td>
<td>1.3 p. 100</td>
<td>–</td>
</tr>
</tbody>
</table>
Other cytotoxic agents
Azathioprine, methotrexate and other cytotoxic agents have been used to treat other vasculitides and can be prescribed to treat RAV. They are reserved for maintenance therapy after stopping CYC–CS and given for a recommended duration of 12 to 18 months. Methotrexate, at a weekly dose of 0.3 mg/kg, can be an effective therapeutic option for minor RAV forms. Alternatively, azathioprine, at the dose of 2 mg/kg/day, can be prescribed.

Plasma exchanges
Although to date no argument supports the systematic prescription of plasma exchanges, they might be useful as second-line therapy or for patients with severe RAV with vascular gangrene or leg arterial ulcers and positive for rheumatoid factor and cryoglobulins.

Biotherapies
Despite the lack of controlled studies, anti-TNFα and rituximab have been used successfully to treat RAV. Several case reports or short case series described clinical responses. Mounting evidence suggests that TNF plays a central role in RAV pathophysiology and, thus, anti-TNFα can be a therapeutic option [24]. The latter study provided evidence of anti-TNFα efficacy in conjunction with CS to treat active refractory RAV. Remission was achieved in 6 patients over 9, which allowed significant CS-sparing; however, these severely ill patients suffered a high infection rate.

Rituximab is also able to induce remissions: complete RAV remission was obtained in most patients receiving rituximab, enabling a significant decrease of the daily prednisone dose along with an acceptable toxicity profile. In the French AutoImmunity and Rituximab Registry [7], which enrolled 1994 RA patients including 17 with rituximab-treated RAV, we observed that, after 6 months of rituximab administration, 12 (71%) patients achieved complete remissions of their vasculitis, 4 had partial responses, and 1 died of uncontrolled vasculitis. All survivors required rituximab or methotrexate maintenance therapy. The relapse rate was higher under methotrexate than rituximab. Under rituximab, we observed that, after 6 months of rituximab administration, 12 (71%) patients achieved complete remissions of their vasculitis, 4 had partial responses, and 1 died of uncontrolled vasculitis. All survivors required rituximab or methotrexate maintenance therapy. The relapse rate was higher under methotrexate than rituximab. Under rituximab, it was possible to taper the steroid dose.

Conclusion
RAV remains one of the most severe forms of systemic vasculitides. Two major changes have been observed in the recent years: first, the progressive decline of its frequency, probably due to improved treatments for RA, like the more frequent use of biotherapies. Second, since the advent of biologics and the more frequent prescription of anti-TNFα or rituximab, the RAV prognosis has been improving. Biotherapies do not replace cytotoxic agents and CS which are still indicated. The combination of biotherapies and immunosuppressants can also be recommended, for example, anti-TNFα and methotrexate.

The progressive disappearance [25] of this RA complication and its better management, attributable to improved therapeutics strategies, are promising.

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References

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S1. Rituximab for ANCA-associated vasculitis: The experience in the United States

In November 1997, rituximab was introduced to the United States (US) market, following approval by the US Food and Drug Administration (FDA) for the treatment of certain B-cell non-Hodgkin lymphomas (table I). This approval represented the FDA’s first licensure of a monoclonal antibody for the treatment of malignant disease, and a contemporary New York Times account touted the agency’s action as a “milestone” and a “turning point” in biotechnology [1,2]. The early post-market-regimen experience with rituximab in B-cell malignancy was highly favorable, as rituximab proved to be both effective and very well tolerated [3]. Within the first few years of its introduction to the US market, the investigational use of rituximab was widely extended, both to a broader range of B-cell malignancies and to a variety of autoimmune diseases that were thought to be mediated by B-cell activity [4]. In 2001, less than 4 years after its introduction to the US market, the first use of rituximab in a patient with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) was reported [5]. AAV refers to a group of syndromes — granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) — that share both the histopathologic feature of necrotizing small-vessel vasculitis and an association with circulating ANCA autoantibodies [6]. All three syndromes are treated with immunosuppression consisting of various combinations of glucocorticoids cyclophosphamide, methotrexate, azathioprine, or mycophenolate mofetil [7]. The index case of rituximab in AAV was a 66-year-old man who had been diagnosed with GPA in 1994 [5]. The treatment options for this patient were limited, as he had previously developed cyclophosphamide toxicity, and prednisone in combination with azathioprine and mycophenolate mofetil had proven ineffective during a disease flare. These limitations prompted the use of rituximab on a compassionate-use basis, under the hypothesis that the actions of rituximab would be particularly well-suited to the treatment of GPA. Rituximab targets the B-lymphocyte-specific cell surface protein CD20, and the binding of rituximab to this protein results in the death of the targeted cell [8,9]. Rituximab induces a remarkable B-cell depletion; following a course of treatment, B-cells typically remain undetectable in the peripheral blood for 6–12 months [10,11]. In GPA, rituximab-mediated B-cell depletion held theoretical promise as a therapeutic strategy, as B-lymphocytes had long been implicated in its pathogenesis [12–14]. The patient promptly achieved remission with the combination of glucocorticoids and rituximab given as four weekly doses of 375 mg/m², the regimen that was FDA-approved for non-Hodgkin lymphoma [5]. Following this favorable outcome, the compassionate-use of rituximab was extended to an additional ten patients with severe refractory AAV (nine with GPA and one with MPA), and clinical remission was achieved in all of these too [11]. Building on these encouraging experiences, the first open-label pilot trial of rituximab for AAV in the US was initiated at the Mayo Clinic in 2003 [15]. Ten patients with active GPA — all of whom had severe, refractory disease — were treated with rituximab accompanied by a protocolized oral glucocorticoid tapering regimen, and all ten patients achieved remission within 3 months.