Treatment practices, response to therapy and adverse events in ANCA-associated vasculitis patients in Europe: top-line findings from a retrospective observational study

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Peter Rutherford
Vifor Pharma Deutschland GmbH

Corresponding Author
ORCiD: https://orcid.org/0000-0003-2425-4358

Dieter Goette
Vifor Pharma Deutschland GmbH

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Abstract

Background ANCA-associated vasculitis patient outcome data in the real world setting is scarce. This study measures key clinical outcomes and adverse effects over the first 12 months of remission induction therapy.

Methods This was a retrospective study of 929 newly diagnosed [ND] and 268 relapsing patients [RP] conducted online by 399 clinicians. Each clinician completed a survey for 3 patients meeting the following criteria: initiated remission induction treatment for new or relapsing disease between Nov 2014 and Feb 2017, ≥ 6 months of therapy including ≥ 1 course of induction therapy, under continuous care for ≥12 months. Data were collected relating to baseline presentation and at 1, 3, 6, and 12 months.

Results 58% were >55 years old with more granulomatosis with polyangiitis (GPA, 54%) versus microscopic polyangiitis (MPA, 46%), and <20% of patients had Birmingham Vasculitis Activity Scoring (BVAS) performed. Median symptom duration prior to diagnosis was 6 to 7 weeks. Presenting symptoms were similar between ND and RP, noted differences (≥ 5%) were more fever, rash, and neuropathy, and less renal disease in RP. The majority (68% ND and 84% RP) had at least one comorbidity at diagnosis, with a similar distribution. Glucocorticoids (GC) were used by 83% ND and 76% RP; >50% were still receiving GC at 12 months. Most common treatments were cyclophosphamide+GC for ND (59%) and rituximab+GC for RP (44%). Many patients had slow and/or partial response to therapy, by 12 months >60% had a full response. 81% of patients with response by month 1 maintained full response through month 12. Adverse events and infections were common, especially during the first 3 months when GC use is highest.

Conclusions Real world data show that both ND and RP ANCA-associated vasculitis patients respond variably to induction remission treatment and many experience adverse events and infections over the first 12 months of treatment. The presence of comorbidities at treatment initiation in most patients compounded the adverse impacts of disease and treatment. This study improves our understanding of the reality of clinical outcomes in ANCA-associated vasculitis and the need for targeted therapeutic approaches.
Background
Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a serious, often life-threatening disease. ANCA-associated vasculitis includes 3 related forms of small-vessel vasculitis: granulomatosis with polyangiitis (GPA, formerly referred to as Wegeners Granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). GPA and MPA have similar clinical phenotypes and characterized by the presence of circulating auto-antibodies against the neutrophil-expressed antigens myeloperoxidase (MPO, mostly seen in MPA) or proteinase 3 (PR3, mostly seen in GPA). GPA and MPA presents with a wide spectrum of manifestations and degrees of severity, ranging from skin lesions, to sino-nasal and pulmonary inflammation, and glomerulonephritis.

It is important to achieve control of active ANCA-associated vasculitis as soon as possible to preserve organ function and avoid cumulative vasculitis and treatment related tissue damage over time [1]. Patients with ANCA-associated vasculitis have a 9-fold increased mortality risk in the first year following diagnosis compared to the general population; which is attributed to infection, active vasculitis, and the effects of renal insufficiency [2]. Current therapies, rather than the underlying disease itself, contribute more than half of this increased risk [3].

The current standard of care in incident ANCA-associated vasculitis patients is to ensure rapid diagnosis and quickly assess comorbidity and vasculitis activity before commencing remission induction treatment. Induction treatments for GPA and MPA rely on substantial immunosuppression, consisting primarily of high-dose glucocorticoids along with either rituximab or cyclophosphamide followed by oral azathioprine [4, 5, 6]. The RAVE study (NCT00104299) showed that the percentage of patients achieving remission (Birmingham Vasculitis Activity Score version 3.0 [BVAS] = 0 and off glucocorticoids) by 6 months was higher with rituximab (67%) compared to cyclophosphamide (42%, P = 0.01), but otherwise similar with respect to adverse events [5]. By 12 months, complete remission without glucocorticoids had dropped to 45 and 47%, respectively, indicating some relapse. By 18 months there were no differences between the 2 therapies with respect to remission rates without need for glucocorticoids, which had fallen further to 39% and 33% [7]. A second smaller study,
RITUXVAS, had similar findings [4].

The vast majority of patients receive glucocorticoids as part of their induction therapy. While glucocorticoids may initially provide a rapid benefit in getting the disease under control, their use is associated with an overall negative impact on patient health due to well-known acute and chronic adverse effects [8]. In ANCA-associated vasculitis, these include increased risk of infection [9, 10, 11], diabetes mellitus, fractures, gastrointestinal bleeding, hypertension, cataract, mental health challenges, and progressive organ damage; the high level of damage associated with glucocorticoid use in ANCA-associated vasculitis has been shown to correlated directly with length of exposure [1].

Relapse in ANCA-associated vasculitis continues to be a major clinical challenge with ≥ 10% ANCA-associated vasculitis patients experiencing relapses of varying severity each year following diagnosis. Relapsing patients are at higher risk of cumulative organ damage from both acute vasculitis and drug related adverse events, and are more likely to relapse again [1]. Long term organ damage from vasculitis and glucocorticoid toxicity are a particular concern, which is directly correlated with mortality [12]. Robson [1], using long term follow up data from patients included in a set of clinical trials, reported that the use of glucocorticoids was highly associated with damage: 47% of patients on glucocorticoids having ≥ 5 areas of damage compared to 23% of patients not on glucocorticoids. Damage was closely correlated with duration of use: 47% of patients on glucocorticoids for 5 years having ≥ 5 items of damage compared to 33% on glucocorticoids for 1 to 18 months; median exposure to glucocorticoids was 36 months (mean 40.4 ± 16.7 months).

However real world data reflecting actual practice in treating ANCA-associated vasculitis in the clinical setting is scarce. To better understand clinical outcomes in clinical practice, a retrospective quantitative data collection study was conducted to measure key clinical outcomes and adverse events and infections in ANCA-associated vasculitis patients in routine clinical practice in Europe.

**Methods**

This was a retrospective quantitative study, conducted with Elma Research Limited (London). A total of 399 physicians, including 240 nephrologists, 120 rheumatologists, and 20 internal medicine physicians (from the United Kingdom, Germany, Italy, and France) contributed. Clinicians who had
been practicing for 2 to 35 years and were actively involved in the treatment and management of ≥10 ANCA-associated vasculitis patients were invited to participate. Physicians were asked to select and complete online patient record forms on 3 of their patients meeting the following criteria: 1) must have been initiated on treatment for a new or relapsing episode of ANCA-associated vasculitis (GPA or MPA) between November 2014 and February 2017, 2) had ≥ 6 months of therapy including ≥ 1 course of induction therapy, and 3) under continuous care by the physician for ≥ 12 months as documented by the clinician relative to baseline presentation, diagnosis and start of remission induction therapy. Both newly diagnosed (first induction treatment) and relapsed (induction treatment following relapse) patients were included. Patients who died during the timeframe specified above could be included (although no deaths were reported in the final database). Data were collected relative to baseline presentation (start of induction therapy) with new ANCA-associated vasculitis or at time of relapse along with outcomes at 1, 3, 6, and 12 months following baseline.

Since it was hypothesized that only a minority of patients would have recorded BVAS scores [13, 14], a three point classification of treatment response was also utilized: full response (no ANCA-associated vasculitis activity and glucocorticoid taper on track), partial response (reduction in ANCA-associated vasculitis activity and major organ damage arrested), or no response (no improvement in ANCA-associated vasculitis activity). Likewise disease severity was categorized as mild (localized disease with no systemic symptoms), moderate (systemic disease with lung and/or renal involvement), or severe (rapidly progressive systemic disease with lung and/or kidney involvement).

Descriptive statistics were used to analyze the data. To analyze the results, patients were divided into two groups: newly diagnosed and relapsed patients. For each subgroup, incidence rates were calculated by the number of patients with the designated outcome divided by the total number of patients in that subgroup.

Results

Baseline Characteristics

A total of 1,197 patient record forms were submitted, with the majority of patients (78%) being newly diagnosed. In general, patient characteristics were similar for both newly diagnosed and relapsed (Table 1 and Table 2). The majority of patients were over 55 years old, slightly more were diagnosed
with GPA vs MPA, and more patients were PR3+ vs MPO+. The data confirmed that in clinical practice BVAS is not used frequently to diagnose disease severity; <20% of patients reported BVAS scores. Of note, more relapsed patients were unemployed or retired compared to newly diagnosed patients, suggesting the disease has an impact on ability to work.

In newly diagnosed patients, median symptom duration was 6 weeks prior to diagnosis, with 16% having symptoms for > 12 weeks. For relapsed patients the time was slightly longer, median time from onset of symptoms to diagnosis was 7 weeks and 20% had symptoms for >12 weeks. For the majority of relapsed patients (63%) this was their first relapse. Presenting symptoms were similar between newly diagnosed and relapsed patients, with noted differences (≥ 5%) in fever, rash and neuropathy and nerve pain, which were higher in relapsed patients. Renal disease was higher in newly diagnosed patients (Table 2).

At the time of diagnosis, most patients also had comorbidities (Figure 1), less than one third of patients reported no comorbidities: 32% of the newly diagnosed and 16% of relapsed patients. The distribution of comorbidities was similar for both groups: hypertension was the most frequently reported comorbidity. Among relapsed patients, most had multiple comorbidities present at the time of the incident vasculitis episode used as the baseline for this study (mean 1.9).

Organ/tissue involvement of the ANCA-associated vasculitis showed a typical distribution with renal and lung involvement being commonly observed (Figure 2) and most patients having multiple organ involvement (median 1.8 for newly diagnosed patients). The pattern of organ involvement was similar for newly diagnosed and relapsed patients.

Table 1: Baseline Patient and Disease Characteristics
| Parameter                               | Variable                     | Newly Diagnosed (N=929, 77.6%) | Relapsed (N=268, 22.4%) |
|-----------------------------------------|------------------------------|--------------------------------|-------------------------|
| Age                                     | Mean                         | 56.8 ± 14.2                    | 58.3 ± 13.1             |
|                                         | 16 - 35                      | 8.5%                           | 4.8%                    |
|                                         | 36 - 45                      | 13.8%                          | 11.9%                   |
|                                         | 46 - 55                      | 20.6%                          | 23.1%                   |
|                                         | 56 - 65                      | 28.5%                          | 29.1%                   |
|                                         | 66 - 75                      | 19.7%                          | 20.9%                   |
|                                         | >75                           | 8.5%                           | 9.7%                    |
| Sex                                     | Male (%)                     | 53.7                           | 60.1                    |
| Education Level (%)                     | Primary school               | 5.7                            | 6.0                     |
|                                         | Secondary/ high school       | 45.5                           | 46.6                    |
|                                         | University                   | 30.7                           | 24.3                    |
|                                         | Unknown                      | 7.4                            | 5.6                     |
| Employment status                       | Working full time            | 36.8                           | 23.5                    |
|                                         | Working part-time            | 15.2                           | 19.8                    |
|                                         | Unemployed                   | 7.1                            | 8.6                     |
|                                         | Retired                      | 31.9                           | 35.4                    |
|                                         | Disabled                     | 1.6                            | 7.1                     |
|                                         | Unknown                      | 7.4                            | 5.6                     |
| Type of ANCA-associated vasculitis      | MPA                          | 45.6                           | 45.9                    |
|                                         | GPA                          | 54.4                           | 54.1                    |
| Antibody Status                         | MPO +                        | 40.6                           | 46.3                    |
|                                         | PR3+                         | 48.3                           | 54.1                    |
| Disease severity level at diagnosis     | Mild                         | 12.2                           | 9.3                     |
|                                         | Moderate                     | 54.3                           | 62.7                    |
|                                         | Severe                       | 33.6                           | 28.0                    |
| BVAS score at diagnosis                 | Mean                         | 24.9 ± 17.5                    | 18.35 ± 14.3            |
|                                         | Median                       | 19.7                           | 14.5                    |
|                                         | Not recorded (%)             | 88.1                           | 82.8                    |
| Duration of symptoms prior to diagnosis | 1-4 weeks                   | 37.9                           | 30.2                    |
|                                         | 5-8 weeks                    | 24.4                           | 15.7                    |
|                                         | 9-12 weeks                   | 11.2                           | 13.1                    |
|                                         | >12 weeks                    | 10.4                           | 19.8                    |
|                                         | Don’t know                   | 10.7                           | 21.3                    |
| Initial treatment prescribed            | Medication                   | 100%                           | 100%                    |
|                                         | Plasma exchange              | 23.4%                          | 16.0%                   |
| Hospitalized at diagnosis              | % Hospitalized               | 68.9                           | 59.7                    |
|                                         | Mean number of days          | 14.6 ± 10.4                    | 13.3 ± 10.1             |

BVAS = Birmingham Vasculitis Activity Score; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PR3 = proteinase 3

Table 2 Presenting Symptoms at Baseline
| Parameter                      | Variable            | Newly Diagnosed (N=929, 77.6%) | Relapsed (N=268, 22.4%) |
|--------------------------------|---------------------|-------------------------------|------------------------|
| **Symptoms**                   |                     |                               |                        |
|                                | Fever               | 53.7%                         | 61.6%                  |
|                                | Rash                | 34.6%                         | 39.6%                  |
|                                | Nasal symptoms      | 34.3%                         | 37.3%                  |
|                                | Haemoptysis         | 30.9%                         | 31.0%                  |
|                                | Musculoskeletal pain| 43.9%                         | 44.4%                  |
|                                | Weight loss         | 52.5%                         | 48.9%                  |
|                                | Joint pain          | 47.1%                         | 48.5%                  |
|                                | Neuropathy & nerve pain | 14.6%                | 21.3%                  |
|                                | Renal failure       | 63.6%                         | 56.3%                  |
|                                | Fatigue             | 57.6%                         | 57.5%                  |
|                                | Other               | 6.50%                         | 9.30%                  |
|                                | None                | 0.60%                         | 0                      |
|                                | Not reported        | 1.50%                         | 3.00%                  |
| **Haematuria**                 | Positive            | 62.0%                         | 59.0%                  |
|                                | Negative            | 21.6%                         | 25.4%                  |
|                                | Not reported        | 16.4%                         | 15.7%                  |
| **Proteinuria (mg/24h)**       | 0                   | 3.0%                          | 2.6%                   |
|                                | 1 - 250             | 22.5%                         | 25.0%                  |
|                                | 251 - 500           | 10.10%                        | 7.50%                  |
|                                | 501-1000            | 12.1%                         | 14.6%                  |
|                                | >1000               | 26.1%                         | 20.1%                  |
|                                | Not reported        | 25.5%                         | 29.5%                  |
| **Estimated glomerular filtration rate Stage (mL/min)** | 1 (≥ 90) | 5.8% | 5.6% |
|                                | 2 (60-89)           | 14.6%                         | 17.5%                  |
|                                | 3a (45-59)          | 13.7%                         | 16.8%                  |
|                                | 3b (30-44)          | 14.9%                         | 18.7%                  |
|                                | 4 (15-29)           | 19.2%                         | 16.0%                  |
|                                | 5 (<15)             | 15.3%                         | 9.0%                   |
|                                | Not reported        | 16.6%                         | 16.4%                  |
| **C-Reactive protein (mg/L)**  | ≤25                 | 24.0%                         | 26.5%                  |
|                                | 26-50               | 17.2%                         | 20.5%                  |
|                                | 51-75               | 14.0%                         | 12.3%                  |
|                                | 76-100              | 10.8%                         | 10.8%                  |
|                                | >100                | 16.9%                         | 12.0%                  |
|                                | Not reported        | 17.2%                         | 17.9%                  |

**Induction Therapy**

The majority of patients in both groups were hospitalized at some point during their induction therapy with long hospitalization (mean 17.3 ± 10.7 days, median 14.3 days), whether newly diagnosed or relapsed (Table 1). Newly diagnosed patients were more likely to receive plasma exchange (23.4%) compared to relapsed patients (16%). Cyclophosphamide with glucocorticoids was the most common
treatment for newly diagnosed patients while for relapsed patients rituximab was used more often (Table 3). The use of other therapies including azathioprine, mycophenolate mofetil, or methotrexate was low (<10% each) in both populations and was more frequently used in patients with less severe symptoms and in relapsed patients.

Table 3  Induction Medications Used

| Medication            | Newly Diagnosed (N=929, 77.6%) | Relapsed (N=268, 22.4%) |
|-----------------------|---------------------------------|-------------------------|
| Cyclophosphamide      | 59.2%                           | 35.1%                   |
| Rituximab             | 24.4%                           | 44.0%                   |
| Glucocorticoids       | 82.6%                           | 76.5%                   |
| Azathioprine          | 6.50%                           | 6.7%                    |
| Mycophenolate Mofetil | 3.10%                           | 7.5%                    |
| Methotrexate          | 6.40%                           | 8.6%                    |
| Other                 | 1.9%                            | 0.7%                    |

The majority of patients continued to receive treatment through the 12 month follow up period, with < 20% discontinuing treatment (Table 4). The majority of patients had their glucocorticoid dose decreased over the 12 month observation period but approximately half of the patients (53%) were still on glucocorticoids at month 12, the majority were on ≤ 10 mg/day (89%) (Table 5).

Table 4  Medication Use over the 12 Month Observation Period

| Month | Newly Diagnosed (N=929) | Relapsed Patients (N = 268) |
|-------|-------------------------|-----------------------------|
|       | New                     | Rel.                        |
|       | 1           | 3     | 6     | 12    | 1     | 3     | 6     |
| Cyclophosphamide | 55% | 39% | 23% | 16% | 32% | 23% | 17% |
| Rituximab       | 24% | 23% | 22% | 21% | 41% | 38% | 36% |
| Azathioprine    | 8%  | 15% | 24% | 25% | 6%  | 10% | 12% |
| Glucocorticoids | 82% | 79% | 67% | 53% | 77% | 71% | 62% |
| Treatment stopped | <1% | 3%  | 13% | 22% | < 1%| 4%  | 12% |

Table 5  Glucocorticoid Use at Month 12 of the Observation Period

| Glucocorticoid Dose (mg/day) | Newly Diagnosed (N=498, 53%) | Relapsed Patients (N=113, 53%) |
|-------------------------------|------------------------------|---------------------------------|
| < 5                           | 34%                          | 27%                             |
| 5 to 10                       | 56%                          | 60%                             |
| >10 to 20                     | 9%                           | 11%                             |
| >20                           | 2%                           | 2%                              |

Response to Induction Therapy

Response to induction therapy was variable and by month 12 slightly more than half the patients in
either group still had a full response (Table 6, Figure 3). Of note, the majority of patients (81%) who achieved an early full response by month 1 maintained that full response through to month 12 (Table 7).

**Table 6  Response to Treatment by Month following Start of Induction Therapy**

| Month | Newly Diagnosed (N=929) | Relapsed Patients (N = 268) |
|-------|--------------------------|-----------------------------|
|       | N | 1 | 3 | 6 | 12 | 1 | 3 | 6 |
| N     | 752 | 929 | 929 | 809 | 201 | 268 | 268 |
| Full response | 22% | 43% | 61% | 68% | 18% | 40% | 57% |
| Partial response | 69% | 49% | 32% | 27% | 71% | 530% | 37% |
| No response | 9% | 7% | 7% | 6% | 10% | 7% | 6% |

**Table 7  Month 1 Response as a Predictor of Response at Month 12**

| Newly diagnosed | Relapsed patients |
|-----------------|-------------------|
| Response at month 1 (N=752) | Percentage of patients who achieved full response at month 12 | Response at month 1 (N=201) | Percentage of patients who achieved full response at month 12 |
| Full response | 164 (22%) | 133 (81%) | 37 (18%) | 30 (15%) |
| Partial response | 518 (69%) | 302 (58%) | 143 (71%) | 70 (35%) |
| No response | 70 (9%) | 14 (20%) | 21 (10%) | 8 (4%) |

Since the number of reported BVAS scores was expected to be low (and proved to be the case at <20%), a four point score was used to assess vasculitis activity at the end of the study period (Table 8). By the end of the follow up period, vasculitis activity was in remission or localized only for most patients but a significant minority of both new and more particularly relapsed patients had persistent active systemic vasculitis. In those patients with BVASv.3 scores, at the end of the 12 month period the median scores were 0.46 (mean 5.3 ± 9.4) for newly diagnosed patients and 2.6 (7.8 ± 15) for relapsed patients, representing a 98% and 82% decrease from median initial assessment, respectively.

**Table 8  Vasculitis Activity at End of 12 months of Treatment**

|  | Newly Diagnosed | Relapsed Patients |
|---|-----------------|-------------------|
|  | N = 790 | N = 206 |
| Moderate to severe - systemic | 6% | 9% |
| Mild to moderate - systemic | 10% | 24% |
| Localized only | 17% | 24% |
| None | 67% | 43% |

**Adverse Events, Infections, and Hospitalizations**
In this retrospective observational study the majority of patients experienced one or more adverse effects, noteworthy in that unlike a controlled clinical trial patients were not surveyed on an ongoing basis, and thus these adverse effects had to be of clinical significance to be recorded.

Adverse events and infections were common, especially during the first 3 months after starting induction therapy (Figure 3). This was not unexpected since it is the time period when glucocorticoid use was highest (Table 4), and occurred with similar frequency between groups (Table 9). Along with infections, the most frequently reported adverse events were changes in red and white blood cell counts. The onset and/or worsening of diabetes also occurred in approximately 10% of patients in both groups in the first months; consistent with the use of glucocorticoids at high dose. Likewise, cataracts and bone events which can be an adverse event glucocorticoids [1], increased in prevalence over the 12 month period.

Table 9 Incidence of Selected Adverse Events and Infections Reported at Any Time Point

| Percent of Patients | Newly Diagnosed (N=929) | Relapsed Patients (N =) |
|---------------------|--------------------------|-------------------------|
| Month               | 1 | 3 | 6 | 12 | 1 | 3 | 6 | 1 | 3 | 6 |
| Adverse Events      |   |   |   |    |   |   |    |   |   |   |
| Cataract formation  | 0.5% | 1.9% | 2.9% | 3.3% | 0.4% | 1.9% | 3.7% |
| New onset diabetes  | 5.3% | 2.3% | 1.4% | 1.2% | 2.6% | 2.2% | 1.1% |
| Worsening of diabetes | 5.3% | 5.9% | 5.1% | 3.4% | 7.5% | 7.8% | 4.9% |
| Bone related events\(^1\) | 1.8% | 2.6% | 1.9% | 2.9% | 1.9% | 4.1% | 5.2% |
| Peptic Ulceration   | 3.4% | 3.0% | 2.2% | 1.6% | 3.4% | 5.6% | 5.6% |
| Hypertension        | 19.5% | 17.1% | 14.9% | 11.4% | 19.4% | 18.3% | 13.8% |
| Cardiac failure     | 3.7% | 3.3% | 2.4% | 1.7% | 3.7% | 5.2% | 4.9% |
| Kidney disease      | 8.7% | 6.7% | 6/6% | 5.5% | 6.0% | 10.8% | 7.5% |
| Bladder symptoms    | 2.2% | 1.6% | 1.2% | 0.8% | 0.4% | 2.2% | 1.5% |
| Leucopaenia         | 12.9% | 9.4% | 5.7% | 4.0% | 13.4% | 13.1% | 7.1% |
| Anemia              | 21.5% | 17.2% | 12.7% | 10.2% | 16.4% | 17.9% | 14.9% |
| Allergic reaction   | 1.3% | 1.2% | 0.6% | 0.3% | 0.7% | 1.5% | 0.4% |
| Low \(\gamma\)-globulins (<3g/L) | 2.0% | 2.4% | 2.5% | 1.9% | 3.4% | 4.5% | 4.5% |
| Change in viral infection status\(^2\) | 0.6% | 0.8% | 0.3% | 0.3% | 0.4% | 1.1% | 1.1% |
| Other               | 2.2% | 3.2% | 3.1% | 2.0% | 1.9% | 2.6% | 1.5% |
| None                | 36.0% | 57.7% | 64.9% | 57.4% | 34.3% | 47.8% | 57.1% |
| No data\(^3\)       | 19.1% | 0 | 0 | 12.9% | 25.0% | 0 | 0 |
| Infections (Q39)    |   |   |   |    |   |   |    |   |   |   |
| Upper Respiratory   | 10.9% | 11.1% | 9.0% | 9.0% | 14.2% | 14.2% | 10.8% |
| Lower Respiratory   | 9.5% | 8.3% | 6.2% | 4.8% | 9.0% | 7.8% | 7.5% |
| Urine               | 11.1% | 10.5% | 7.4% | 6.7% | 11.9% | 11.9% | 8.6% |
| No infections       | 53.5% | 72.3% | 76.9% | 67.2% | 46.6% | 69.8% | 73.5% |
| No data\(^3\)       | 19.1% | 0 | 0 | 12.9% | 25.0% | 0 | 0 |
1. Fracture, osteoporosis, aseptic necrosis
2. Hepatitis B, Hepatitis C, herpes
3. Patient was not seen or assessed at this time point.

Discussion

Baseline disease state and Comorbidities

This retrospective observational study examined real world outcomes in ANCA-associated vasculitis in patients, both newly diagnosed and relapsing, who required remission induction therapy in Europe. Outcomes reported here are consistent with previously reported randomized clinical trials, and provide new insights into the burden of ANCA-associated vasculitis.

The majority of patients were symptomatic for at least 1 to 3 months prior to diagnosis, a few were symptomatic for up to 5 years suggesting the disease is difficult to diagnosis in the primary care setting. Similar times to diagnosis were observed in previous EU studies [15, 16] and are associated with adverse long term clinical outcomes [16]. A detailed examination of primary care visits prior to GPA diagnosis [16] found that although the frequency of consultations, particularly for nasopharyngeal symptoms was higher in the 12 months prior to diagnosis, predictive approaches would be unlikely to be useful. The observation that more patients who developed GPA had visits to secondary care in that time compared to control patients [16] points to the need for wider awareness of ANCA-associated vasculitis in emergency room and other medical specialty staff.

Most patients had ≥1 comorbidity at diagnosis confirming results of previous studies [3, 17, 18] who also found that majority of patients had comorbid diseases including important cardiovascular diseases [18]. Some studies have demonstrated comorbidity at diagnosis is one factor determining long term survival [17, 18] but another study suggested the patients functional status, which would be influenced by comorbidity is more predictive [3]. Two other factors relating to comorbidity should be considered, firstly ANCA-associated vasculitis treatment could worsen or progress specific comorbidities. For instance the impact of high dose glucocorticoids on glucose intolerance or diabetes mellitus, existing bone disease, and cardiovascular risk is important. Secondly, it may be hard to distinguish clinically comorbid illness from acute vasculitis and from chronic vasculitis damage over
Evidence for this is illustrated in Figure 1 where newly diagnosed patients had fewer comorbidities and lower frequencies of most comorbidities (type 1 diabetes the one exception) compared to relapsing patients. The pattern of organ involvement in this study of real-world patients was similar to that in patients from real-world studies and clinical trials [19] although reflecting the representation of many nephrologists in the current study so patients with renal disease were possibly enriched. In the relapsed group more patients had involvement of lung, skin, and nerves, with other organs being similarly impacted in both groups. Monitoring the patient regularly during the maintenance phase should allow detection of relapse at an earlier stage so that less severe disease and lower organ involvement should be expected.

Response rates

A key principle of ANCA-associated vasculitis clinical management is to achieve rapid control of the vasculitis activity. BVAS is a clinical index for disease assessment developed in 1994 [20] and last updated in 2009 to version 3.0 [13]. Symptoms covering 9 organ systems that are attributable to vasculitis are checked if they are present currently or occurred within the last month, and/or if they are persistent. They survey takes only a few minutes to complete but does require training and it is essential to only score acute/ongoing symptoms and signs, not fixed damage from vasculitis or comorbidity. The BVAS scoring system is the gold standard for assessing vasculitis disease activity in clinical trials and has been shown to have prognostic value and correlate with mortality risk assessment [21, 22]. It was hypothesized that this was not used routinely in clinical practice and this was confirmed since <20% had BVAS scores reported. Given the likely lack of BVAS scores, disease response and severity were assessed on a 3-point scale (Table 6). Using these criteria, response to remission induction therapy was variable with many patients taking several months to achieve full or partial response. Patients achieving a full response at one month were more likely to have a full response rate at month 12 (Table 7). A recent reanalysis of a set of EUVAS trials also demonstrated that achieving BVAS remission by 6 months was associated with improved long-term outcomes and survival [23]. The current data also showed the importance of assessing early response at month 1 although the amount of missing data at this time point suggests service improvement may be needed.
to ensure this is done.

Full response was achieved by $\leq 61\%$ of patients at any time point with a peak response by month 6 with more than $90\%$ of patients achieving a full or partial response. The data suggest that approximately $10\%$ of these patients then relapsed between months 6 and 12. These results ($60\%$ had full response at month 6 [no ANCA-associated vasculitis activity and glucocorticoid taper on track]) are consistent with the RAVE study where $61\%$ of patients on rituximab and $63\%$ of patients on cyclophosphamide achieved complete remission ($\text{BVAS} = 0$ and off prednisone) by month 6 [7], and the MYCYC study where $61\%$ and $67\%$ of patients achieved remission by month 6 on cyclophosphamide or mycophenolate mofetil, respectively [24]. Also consistent was the relapse by month 12; in the RAVE study complete remission ($\text{BVAS} = 0$ and off prednisone) had fallen to $45\%$ on rituximab and $47\%$ on cyclophosphamide/azathioprine [7], versus $57\%$ with full response in this observational study where some patients were still receiving glucocorticoids. There are still unmet needs in achieving and maintaining remission in ANCA-associated vasculitis with current therapies and a significant minority of patients have ongoing vasculitis activity. In addition patient monitoring and the utility of disease assessment tools in routine practice need to be considered. This is not only relevant for assessing vasculitis activity but also for assessing and discriminating chronic vasculitis damage using the Vasculitis Damage Index [1] and for measuring the size, impact and changes in glucocorticoid toxicity using the glucocorticoid toxicity index [25].

**Adverse Effects and Toxicities**

Reported therapy-related adverse events and infections were common, especially in the first 3 months when patients are still getting into remission and still receiving high dose glucocorticoids. The observed results are consistent with the literature in that the majority of the adverse events and infections reported can be attributed to the use of glucocorticoid and immunosuppressive therapies, rather than the underlying vasculitis [3]. A variety of adverse events were reported and the frequently observed hypertension is an important cardiovascular risk factor which must contribute to the elevated long-term increased mortality risk from cardiovascular disease in ANCA-associated vasculitis [26]. The pattern of other potentially glucocorticoid-related adverse events followed that observed in
a recent systematic literature review [27]. Some risks were acute, for instance the observation of new onset diabetes at the start of therapy with high dose versus the more chronic impact of longer term use in terms of cataract formation and bone disorders. Interestingly the present study confirmed others [28] who observed that a significant minority of patients remain on glucocorticoids at 12 months. Recently published data confirm that even a relatively low dose is associated with important adverse clinical outcomes [29, 30] and must not be accepted or ignored.

The present study also illustrates of the frequency of haematological changes in the first few months of therapy related to the combination of immunosuppressants and glucocorticoids. In addition an important incidence of hypogammaglobulinemia was observed especially in relapsing patients. This adverse event is often linked to the use of Rituximab and is more commonly seen now with wider use [31] of the drug and is another factor linked to increased risk of infection [31].

Strengths of this study are based on the source being reflective of contemporaneous real world clinical practice in Europe, based on practice patterns established around and following the joint EULAR/ERA-EDTA clinical guidance [6]. It is a multicenter study performed across 4 different countries and its wide inclusion criteria across >1000 patients allows clarity and generalizability. Weaknesses also reflect the real world nature of the data and its capture, with physician selection of a “convenience” sample for data collection. That data collection was limited in nature to encourage completion and there was no formal data monitoring so missing data items is a challenge. Overall the data set is consistent with previous clinical trials and studies and brings new insight for clinical practice.

Conclusions
This analysis of real world clinical practice confirm there is an unmet medical need in both incident and relapsing ANCA-associated vasculitis patients related to achieving improved full response rates and reducing the toxicity of therapy in terms of acute complications and long term organ damage. Preexisting co-morbidities are common and will impact treatment decisions and clinical outcomes. Assessment of response to therapy and achieving early full control of vasculitis activity is important and using robust simple but robust disease activity scores might be useful in more effectively
managing patients and in making treatment decisions. There is a need for new therapy options to achieve rapid and complete remission while preserving organs and avoiding adverse events and infections.

List Of Abbreviations

ANCA
Anti-neutrophil cytoplasmic antibody

BVAS
Birmingham Vasculitis Activity Score

GPA
Granulomatosis with polyangiitis

MPA
Microscopic polyangiitis

MPO
Myeloperoxidase

PR3
Proteinase 3

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Declarations

Ethics Approval and Consent to Participate: Elma Research is an independent market research agency working within Market Research Society (MRS), British Healthcare Business Intelligence Association (BHBIA), and Association of British Pharmaceutical Industry (ABPI) guidelines. This work was performed as a market research activity and it complied with all EU laws protecting personal data, and also in accordance with the EphMRA and BHBIA market research codes of conduct.

Consent for publication: Not applicable

Availability of data and materials: The dataset analyzed for the study reported here is available
from the corresponding author on reasonable request.

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**Authors’ Contribution:** PR and DG developed the questionnaire used, analysed and interpreted the data. PR was a major contributor in the writing of the manuscript. All authors read and approved the final manuscript.

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**Figures**

![Figure 1](image-url)

**Figure 1**

Co-Morbidities at Diagnosis
Figure 2
Organ involvement at Diagnosis

Figure 3
Response to treatment by Month Denominator used was entire population regardless if they were seen that month or not: Newly diagnosed \(n=929\), relapsed \(n=269\).