



**SPANISH REGISTRY ON ADVERSE EVENTS OF BIOLOGICAL THERAPIES
IN RHEUMATIC DISEASES**

(Phase II)

DECEMBER 2015 REPORT

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Description of the Registry with all the Biological Therapies

BIOBADASER 2.0 downloading of data took place on November 17th 2015. Ten centers participate in this project. Due to work overload, the *Hospital La Fe de Valencia* ended its participation in 2010, as did the *Hospital de la Princesa* and the *Hospital 12 de Octubre de Madrid*, both at the beginning of 2013; the *Hospital Gregorio Marañón* also ended its participation later in 2013 because the principal investigator could no continue with the project. As of today, 7,132 have been included, totaling the administration of 26,629 cycle treatments. See **Table 1** for a description of the patients included.

Table 1.- Description of patients included in BIOBADASER 2.0

| All Biological Agents | | | |
|---|----------------------|---|----------|
| Number of Patients (%) | 7,132 | | |
| Women (%) | 4,416 (61.9) | | |
| Mean Age (SD) | 57.9 (15.8) | | |
| Mean Age of First Biological Treatment Start (SD) | 48.7 (15.3) | | |
| Median Time (in Years) (P ₅₀) Since Disease Onset by Beginning of Treatment [P ₂₅ -P ₇₅] | 9.0 [4.1-16.0] | | |
| Diagnosis | n (%) | | n (%) |
| Rheumatoid Arthritis | 3,603 (50.5) | Polymyositis / Dermatomyositis | 18 (0.3) |
| Ankylosing Spondylitis | 1,182 (16.6) | Juvenile Undifferentiated Spondyloarthritis | 17 (0.2) |
| Arthritis or Psoriatic Spondyloarthritis | 1,133 (15.9) | Reactive Arthritis | 16 (0.2) |
| Undifferentiated Spondyloarthropathy | 297 (4.2) | SAPHO Syndrome | 15 (0.2) |
| Juvenile Idiopathic Arthritis | 293 (4.1) | Scleroderma | 11 (0.2) |
| Enteropathic Arthritis | 138 (1.9) | Relapsing Polychondritis | 10 (0.1) |
| Systemic Lupus Erythematosus | 62 (0.9) | Psoriasis | 9 (0.1) |
| Seronegative Chronic Polyarthritis | 47 (0.7) | Sarcoidosis | 9 (0.1) |
| Behçet's Disease | 45 (0.6) | Pyoderma Gangrenosum | 2 (0.0) |
| Overlap Syndrome | 44 (0.6) | Muckle-Wells Syndrome | 2 (0.0) |
| Uveitis With No Rheumatic Disease | 38 (0.5) | Felty's Syndrome | 1 (0.0) |
| Seronegative Chronic Oligoarthritis | 37 (0.5) | Epidermolysis Bullosa | 1 (0.0) |
| Vasculitis | 27 (0.4) | Relapsing Hidradenitis | 1 (0.0) |
| Still's Disease | 26 (0.4) | CINCA syndrome | 1 (0.0) |
| Primary Sjögren's Syndrome | 25 (0.4) | Felty's syndrome | 1 (0.0) |
| Juvenile Ankylosing Spondylitis | 21 (0.3) | Eosinophilic Fasciitis | 1 (0.0) |
| Total | 7,132 (100.0) | | |

The registry consists mainly of middle-aged women with a median disease progression before beginning biologic treatment of 9.0 years with an interquartile range of 11.9 years. The most frequent diagnosis is rheumatoid arthritis (50.5%), followed by ankylosing spondylitis (16.6%), and psoriatic arthritis (15.9%).

Table 2 shows the description of the cycle treatments. We divided the data according to whether therapy was used as the first treatment option, or as second option, or a later option, i.e. the patient has had at least one prior biological therapy which was discontinued, except for rituximab, for which, given its protocol, second cycles are considered, even when treatment has not been suspended. From all treatment cycles reported, 54.7 % (14,564) are biologics used as the first treatment option.

Table 2.- Description of Biological Treatments

| Biological Agent | First Option Treatment n (%) | As Second or Later Option Treatment n (%) | All n (%) |
|------------------------------------|---------------------------------|--|--------------|
| Etanercept | 3,954 (27.2) | 3,097 (25.7) | 7,051 (26.5) |
| Infliximab | 6,357 (43.7) | 1,242 (10.3) | 7,599 (28.5) |
| Adalimumab | 3,142 (21.6) | 2,322 (19.3) | 5,464 (20.5) |
| Anakinra | 53 (0.4) | 89 (0.7) | 142 (0.5) |
| Rituximab | 377 (2.6) | 3,316 (27.5) | 3,693 (13.9) |
| Abatacept | 137 (0.9) | 635 (5.3) | 772 (2.9) |
| Tocilizumab | 393 (2.7) | 892 (7.4) | 1,285 (4.8) |
| Ocrelizumab | 0 (0.0) | 4 (0.0) | 4 (0.0) |
| Golimumab | 101 (0.7) | 316 (2.6) | 417 (1.6) |
| Certolizumab | 48 (0.3) | 124 (1.0) | 172 (0.7) |
| Canakinumab | 0 (0.0) | 15 (0.1) | 15 (0.1) |
| Belimumab | 2 (0.0) | 1 (0.0) | 3 (0.0) |
| Ustekinumab | 0 (0.0) | 12 (0.1) | 12 (0.1) |
| Treatment Cycles | 14,564 (100) | 12,065 (100) | 26,629 (100) |
| Reason for Discontinuation | n (%) | n (%) | n (%) |
| Inefficacy or Loss of Efficacy | 2,797 (32.6) | 2,234 (26.1) | 5,031 (29.3) |
| Adverse Event | 3,576 (41.7) | 2,325 (27.1) | 5,901 (34.4) |
| Pregnancy or Desire to Be Pregnant | 237 (2.8) | 139 (1.6) | 376 (2.2) |
| Patient Lost | 343 (4.0) | 146 (1.7) | 489 (2.9) |
| Remission | 420 (4.9) | 113 (1.3) | 533 (3.1) |
| Other | 1,169 (13.6) | 3,530 (41.2) | 4,699 (27.4) |
| Unknown | 35 (0.4) | 85 (1.0) | 120 (0.7) |
| Total Number of Discontinuations | 8,577 (100) | 8,572 (100) | 17,149 (100) |

Biologic agents most frequently used as first option are infliximab (43.7%) and etanercept (27.2%). Rituximab (27.5%), etanercept (25.7%) and adalimumab (19.3%) are the ones most often used as the

second or later treatment option. The substantial increase in the use of rituximab as second or later biologic treatment option, is due to its different administration protocol. Two cycles of rituximab 6 months apart –the usual timeline for this biologic– are considered separate treatments, unlike with infliximab, as an example of another intravenously administered biologic. Tocilizumab y golimumab increase their utilization.

Among the reasons for discontinuation of treatment with the first-option biologic, occurrence of an adverse event is the most reported one accounting for 41.7%, followed by inefficacy or loss of efficacy (32.6%). In second or later treatments, disregarding the category “other” which refers to the end of rituximab cycle, it adverse events (26.1%) and inefficacy or loss of efficacy (27.1%).

Following the trend of recent years, the number of discontinuations has remained high due to ‘other’ reasons, something that may well be because of the way of administration and accounting method with rituximab treatments, being in this case the end of a cycle without problems.

Table 3 summarizes the frequency and percentage of the different adverse events reported by large organ and systems groups (MedDRA). The most common ones are infections and infestations, accounting for 36.1% of all recorded adverse events, followed by general disorders and administration site reactions with 7.1%.

Table 3.- Frequency of Adverse Events by Group

| Adverse Events (AE) | n | % of Total AE |
|--|-------|---------------|
| Infections and Infestations | 6,760 | 36.3 |
| General Disorders and Administration Site Reactions | 1,315 | 7.1 |
| Skin and Subcutaneous Tissue Disorders | 1,198 | 6.4 |
| Additional Patient Investigations | 861 | 4.6 |
| Gastrointestinal Disorders | 849 | 4.6 |
| Musculoskeletal and Connective Tissue Disorders | 755 | 4.1 |
| Nervous System Disorders | 744 | 4.0 |
| Injury, Poisoning and Complications from Treatment Procedures | 660 | 3.6 |
| Surgical and Medical Procedures | 594 | 3.2 |
| Eye Disorders | 550 | 3.0 |
| Respiratory, Thoracic and Mediastinal Disorders | 529 | 2.8 |
| Neoplasms Benign, Malignant, and Unspecified (Included Cysts and Polyps) | 509 | 2.7 |
| Blood and Lymphatic System Disorders | 457 | 2.5 |
| Vascular Disorders | 455 | 2.5 |
| Cardiac Disorders | 445 | 2.4 |
| Renal and Urinary Disorders | 396 | 2.1 |
| Metabolism and Nutrition Disorders | 340 | 1.8 |
| Psychiatric Disorders | 256 | 1.4 |

| Adverse Events (AE) | n | % of Total AE |
|---|--------|---------------|
| Hepatobiliary Disorders | 255 | 1.4 |
| Reproductive System, and Breast Disorders | 187 | 1.0 |
| Pregnancy, Puerperium, and Perinatal Conditions | 114 | 0.6 |
| Ear and Labyrinth Disorders | 113 | 0.6 |
| Endocrine Disorders | 99 | 0.5 |
| Immune System Disorders | 71 | 0.4 |
| Congenital, Familiar, and Genetic Disorders | 59 | 0.3 |
| Social Circumstances | 32 | 0.2 |
| Total | 18,603 | 100.0 |

Of the adverse events recorded, 84.1% (15,363) were classified as "non-serious," 15.9% (3,240) were reported as "serious," and 1.7% (308) were "fatal."

Table 4 shows the frequency of reported serious adverse events. The most common are still infections and infestations, followed by cardiac disorders and neoplasms.

Table 4.- Frequency of Serious Adverse Events

| Serious Adverse Events (SAE) | n | % of Total SAE |
|--|-------|----------------|
| Infections and Infestations | 1,081 | 33.4 |
| Neoplasms Benign, Malignant, and Unspecified (Included Cysts and Polyps) | 268 | 8.3 |
| Cardiac Disorders | 258 | 8.0 |
| Surgical and Medical Procedures | 220 | 6.8 |
| Injury, Poisoning, and Complications from Treatment Procedures | 180 | 5.6 |
| Nervous System Disorders | 160 | 4.9 |
| General Disorders and Administration Site Reactions | 157 | 4.9 |
| Respiratory, Thoracic, and Mediastinal Disorders | 142 | 4.4 |
| Gastrointestinal Disorders | 128 | 4.0 |
| Vascular Disorders | 88 | 2.7 |
| Renal and Urinary Disorders | 84 | 2.6 |
| Musculoskeletal and Connective Tissue Disorders | 70 | 2.2 |
| Blood and Lymphatic System Disorders | 66 | 2.0 |
| Skin and Subcutaneous Tissue Disorders | 64 | 2.0 |
| Hepatobiliary Disorders | 50 | 1.5 |
| Eye Disorders | 46 | 1.4 |
| Psychiatric Disorders | 33 | 1.0 |
| Metabolism and Nutrition Disorders | 30 | 0.9 |
| Immune System Disorders | 27 | 0.8 |
| Pregnancy, Puerperium, and Perinatal Conditions | 26 | 0.8 |

| | | |
|---|-------|-------|
| Additional Patient Investigations | 24 | 0.7 |
| Reproductive System and Breast Disorders | 17 | 0.5 |
| Endocrine Disorders | 7 | 0.2 |
| Congenital, Familiar, and Genetic Disorders | 6 | 0.2 |
| Social Circumstances | 4 | 0.1 |
| Ear and Labyrinth Disorders | 4 | 0.1 |
| Total | 3,240 | 100.0 |

Table 5 shows the frequency and proportion of fatal adverse events listed by System Organ Classes. Most common causes of death were infections (27.9%), especially pneumonia (4.5%), and sepsis (3.6%). Neoplasms (25.7% frequency) are the second largest group of fatal events followed by cardiac disorders (15.6%), and general disorders (11.0%).

General disorders are found among the fatal adverse events because MedDRA encodes deaths by unknown cause under this category. A table in the appendix lists all the deaths reported in BIOBADASER 2.0.

Table 5.- Frequency of Fatal Adverse Events

| Fatal Adverse Events (FAE) | n | % of Total FAE |
|--|-----|----------------|
| Infections and Infestations | 86 | 27.9 |
| Neoplasms Benign, Malignant, and Unspecified (Included Cysts and Polyps) | 79 | 25.7 |
| Cardiac Disorders | 48 | 15.6 |
| General Disorders and Administration Site Reactions | 34 | 11.0 |
| Nervous System Disorders | 14 | 4.6 |
| Respiratory, Thoracic, and Mediastinal Disorders | 12 | 3.9 |
| Gastrointestinal Disorders | 9 | 2.9 |
| Surgical and Medical Procedures | 8 | 2.6 |
| Injury, Poisoning, and Complications from Treatment Procedures | 5 | 1.6 |
| Blood and Lymphatic System Disorders | 4 | 1.3 |
| Renal and Urinary Disorders | 3 | 1.0 |
| Vascular Disorders | 2 | 0.7 |
| Circunstancias Sociales | 1 | 0.3 |
| Hepatobiliary Disorders | 1 | 0.3 |
| Immune System Disorders | 1 | 0.3 |
| Psychiatric Disorders | 1 | 0.3 |
| Total* | 308 | 100.0 |

* A total of 246 patients died, but some patients suffered more than one fatal adverse event.

Table 6 shows the incidence rate of all adverse events listed by System Organ Class. Total incidence rate is 391.9 (386.4-397.5) adverse events per 1,000 patient-years. For serious adverse events the incidence rate is 81.8 (79.4-84.4) per 1,000 patient-years. For fatal adverse events the incidence rate is 6.2 (5.6-7.0) per 1,000 patient-years per 1,000 patient-years.

Table 6.- Incidence Rate of Adverse Events

| Incidence Rate (95% CI) /x 1,000 Patient-Years | First Option Treatment | Second and Later Option Treatments | Total |
|--|------------------------|------------------------------------|---------------------|
| All Adverse Events | 364.0 (357.4-370.6) | 444.1 (434.3-454.2) | 391.9 (386.4-397.5) |
| Serious | 66.0 (63.3-68.9) | 111.4 (106.5-116.5) | 81.8 (79.4-84.4) |
| Fatal | 4.9 (4.2-5.8) | 8.6 (7.4-10.2) | 6.2 (5.6-7.0) |
| By System Organ Classes | | | |
| Infections and Infestations | 133.0 (129.1-137.1) | 171.1 (165.0-177.4) | 146.3 (142.9-149.7) |
| General Disorders and Administration Site Conditions | 26.6 (24.8-28.4) | 31.8 (29.2-34.5) | 28.4 (26.9-29.9) |
| Skin Disorders | 24.0 (22.3-25.7) | 29.0 (26.6-31.7) | 25.7 (24.3-27.2) |
| Gastrointestinal Disorders | 15.4 (14.1-16.8) | 23.6 (21.4-26.0) | 18.3 (17.1-19.5) |
| Additional Patient Investigations | 17.8 (16.4-19.3) | 17.9 (16.0-20.1) | 17.8 (16.7-19.0) |
| Nervous System Disorders | 14.4 (13.2-15.8) | 22.8 (20.7-25.2) | 17.4 (16.2-18.6) |
| Musculoskeletal Disorders | 14.8 (13.5-16.2) | 21.0 (18.9-23.2) | 16.9 (15.8-18.1) |
| Neoplasms | 13.9 (12.7-15.3) | 22.6 (20.4-24.9) | 16.9 (15.8-18.1) |
| Injury | 12.3 (11.1-13.5) | 20.3 (18.2-22.5) | 15.0 (14.0-16.2) |
| Medical Procedures | 10.5 (9.5-11.7) | 18.3 (16.4-20.4) | 13.2 (12.3-14.3) |
| Respiratory Disorders | 9.4 (8.4-10.6) | 15.6 (13.8-17.5) | 11.6 (10.7-12.6) |
| Eye Disorders | 10.3 (9.3-11.5) | 13.8 (12.2-15.7) | 11.5 (10.6-12.5) |
| Cardiac Disorders | 8.5 (7.6-9.6) | 15.6 (13.8-17.5) | 11.0 (10.1-11.9) |
| Blood Disorders | 8.0 (7.1-9.0) | 15.6 (13.9-17.6) | 10.6 (9.8-11.6) |
| Vascular Disorders | 9.7 (8.7-10.9) | 11.8 (10.3-13.5) | 10.4 (9.6-11.4) |
| Renal and Urinary Disorders | 7.7 (6.8-8.7) | 11.0 (9.5-12.7) | 8.8 (8.0-9.7) |
| Metabolism Disorders | 6.5 (5.7-7.4) | 9.3 (8.0-10.8) | 7.5 (6.7-8.3) |
| Hepatobiliary Disorders | 4.5 (3.8-5.3) | 7.3 (6.1-8.6) | 5.4 (4.8-6.1) |
| Psychiatric Disorders | 4.9 (4.2-5.7) | 6.0 (4.9-7.3) | 5.3 (4.7-6.0) |
| Reproductive System and Breast Disorders | 3.7 (3.1-4.4) | 5.2 (4.2-6.4) | 4.2 (3.7-4.8) |
| Pregnancy, Puerperium, and Perinatal Conditions | 1.9 (1.5-2.5) | 4.2 (3.3-5.3) | 2.7 (2.3-3.2) |
| Ear and Labyrinth Disorders | 2.2 (1.8-2.8) | 2.7 (2.0-3.6) | 2.4 (2.0-2.9) |
| Endocrine Disorders | 2.0 (1.6-2.6) | 2.3 (1.7-3.1) | 2.1 (1.7-2.5) |
| Immune System Disorders | 1.1 (0.8-1.5) | 2.4 (1.8-3.3) | 1.6 (1.2-1.9) |
| Congenital Disorders | 1.2 (0.9-1.7) | 1.5 (1.0-2.2) | 1.3 (1.0-1.7) |
| Social Circumstances | 0.7 (0.5-1.1) | 0.8 (0.5-1.4) | 0.8 (0.6-1.1) |

Table 7 shows the incidence rate of those adverse effects considered serious by the researchers. Serious infections and infestations presented an incidence rate of 25.3 (24.0-26.8) serious adverse events per 1,000 patient-years. Incidence rate for cardiac disorders are 7.3 (6.6-8.1) per 1,000 patient-years, and incidence rate for neoplasms are 10.3 (9.5-11.2) per 1,000 patient-years.

Table 7.- Incidence Rate of Serious Adverse Events

| Incidence Rate (95% CI) /x 1,000 Patient-Years | First Option Treatment | Second and Later Option Treatments | Total |
|--|------------------------|------------------------------------|------------------|
| Infections and Infestations | 21.5 (20.0-23.2) | 32.5 (29.9-35.3) | 25.3 (24.0-26.8) |
| Neoplasms | 8.8 (7.8-9.9) | 13.1 (11.5-14.9) | 10.3 (9.5-11.2) |
| Cardiac Disorders | 5.8 (5.1-6.7) | 10.2 (8.8-11.8) | 7.3 (6.6-8.1) |
| Medical Procedures | 3.8 (3.2-4.6) | 7.3 (6.1-8.6) | 5.0 (4.4-5.7) |
| Injury | 3.3 (2.7-4.0) | 6.1 (5.0-7.4) | 4.3 (3.7-4.9) |
| General Disorders and Administration Site Conditions | 3.0 (2.5-3.7) | 6.4 (5.3-7.7) | 4.2 (3.7-4.8) |
| Nervous System Disorders | 3.3 (2.7-3.9) | 5.3 (4.4-6.6) | 4.0 (3.5-4.6) |
| Respiratory Disorders | 2.5 (2.0-3.1) | 4.7 (3.8-5.8) | 3.2 (2.8-3.8) |
| Gastrointestinal disorders | 2.5 (2.0-3.1) | 4.2 (3.3-5.3) | 3.1 (2.6-3.6) |
| Vascular Disorders | 2.0 (1.5-2.5) | 2.3 (1.7-3.1) | 2.1 (1.7-2.5) |
| Renal and Urinary Disorders | 1.8 (1.4-2.3) | 2.4 (1.8-3.2) | 2.0 (1.6-2.4) |
| Blood Disorders | 0.9 (0.6-1.3) | 3.7 (2.9-4.7) | 1.9 (1.5-2.3) |
| Musculoskeletal Disorders | 1.3 (0.9-1.7) | 2.7 (2.0-3.6) | 1.8 (1.4-2.2) |
| Skin Disorders | 1.0 (0.7-1.4) | 2.1 (1.5-2.9) | 1.4 (1.1-1.7) |
| Hepatobiliary Disorders | 0.8 (0.6-1.2) | 1.6 (1.1-2.4) | 1.1 (0.9-1.4) |
| Eye Disorders | 0.6 (0.4-1.0) | 1.6 (1.1-2.4) | 1.0 (0.7-1.3) |
| Psychiatric Disorders | 0.6 (0.4-1.0) | 0.9 (0.6-1.5) | 0.7 (0.5-1.0) |
| Pregnancy, Puerperium, and Perinatal Conditions | 0.4 (0.2-0.7) | 1.0 (0.7-1.7) | 0.6 (0.4-0.9) |
| Metabolism Disorders | 0.6 (0.4-0.9) | 0.7 (0.4-1.2) | 0.6 (0.4-0.9) |
| Immune System Disorders | 0.4 (0.2-0.7) | 1.0 (0.6-1.6) | 0.6 (0.4-0.8) |
| Additional Patient Investigations | 0.5 (0.3-0.8) | 0.6 (0.4-1.2) | 0.5 (0.4-0.8) |
| Reproductive System and Breast Disorders | 0.3 (0.2-0.6) | 0.3 (0.2-0.8) | 0.3 (0.2-0.6) |
| Congenital Disorders | 0.1 (0.0-0.3) | 0.2 (0.1-0.6) | 0.1 (0.1-0.3) |
| Endocrine Disorders | 0.2 (0.1-0.4) | 0.1 (0.0-0.5) | 0.1 (0.1-0.3) |
| Social Circumstances | 0.1 (0.0-0.3) | 0.2 (0.1-0.5) | 0.1 (0.1-0.3) |
| Ear and Labyrinth Disorders | 0.1 (0.0-0.3) | 0.1 (0.0-0.5) | 0.1 (0.0-0.2) |

APPENDIX

Table I.- Itemized Frequencies of Fatal Adverse Events

| Fatal Adverse Events (FAE) | n | % of Total FAE |
|--|-----------|----------------|
| Infections and Infestations | 75 | 33.5 |
| Pneumonia | 11 | 14.7 |
| Sepsis | 9 | 12.0 |
| Septic Shock | 5 | 6.7 |
| Lower Respiratory Tract Infection | 4 | 5.3 |
| Disseminated Tuberculosis | 4 | 5.3 |
| Bronchial Pneumonia | 3 | 4.0 |
| Staphylococcal Endocarditis | 2 | 2.7 |
| Upper Respiratory Tract Infection | 2 | 2.7 |
| Peritoneal Infection | 2 | 2.7 |
| Staphylococcal Sepsis | 2 | 2.7 |
| Pulmonary Tuberculosis | 2 | 2.7 |
| Brain Abscess | 1 | 1.3 |
| Liver Abscess | 1 | 1.3 |
| Staphylococcus Septic Arthritis | 1 | 1.3 |
| Aspergillosis | 1 | 1.3 |
| Bronchopulmonary Aspergillosis | 1 | 1.3 |
| Vaginal Candidiasis | 1 | 1.3 |
| Diverticulitis | 1 | 1.3 |
| Bacterial Endocarditis | 1 | 1.3 |
| Infectious Spondylitis | 1 | 1.3 |
| Gastroenteritis Due to Clostridium | 1 | 1.3 |
| Visceral Herpes Simplex | 1 | 1.3 |
| Infection | 1 | 1.3 |
| Bacterial Infection | 1 | 1.3 |
| Soft Tissue Infection | 1 | 1.3 |
| Urinary Tract Infection Due to Pseudomonas | 1 | 1.3 |
| Enterococcal Infection | 1 | 1.3 |
| Staphylococcal Infection | 1 | 1.3 |
| Staphylococcal Infection of a Wound | 1 | 1.3 |
| Acinetobacter Infection | 1 | 1.3 |
| Cytomegalovirus Infection | 1 | 1.3 |
| Escherichia Coli Infection | 1 | 1.3 |

| | | |
|---|-----------|-------------|
| Lung Infection | 1 | 1.3 |
| Lobar Pneumonia | 1 | 1.3 |
| Pneumonia Due to Escherichia Coli | 1 | 1.3 |
| Pneumonia Due to Mycoplasma Pneumoniae | 1 | 1.3 |
| Bacterial Peritonitis | 1 | 1.3 |
| Bacterial Pyelonephritis | 1 | 1.3 |
| Sepsis Due to Escherichia Coli | 1 | 1.3 |
| Lymph Node Tuberculosis | 1 | 1.3 |
| Neoplasms Benign, Malignant, and Unspecified (Included Cysts and Polyps) | 52 | 21.1 |
| Adenocarcinoma of the Pancreas | 3 | 5.8 |
| Pancreatic Carcinoma | 3 | 5.8 |
| Breast Xancer | 3 | 5.8 |
| Squamous Cell Lung Carcinoma | 2 | 3.9 |
| Esophageal Carcinoma | 2 | 3.9 |
| Malignant Neuroendocrine Carcinoma | 2 | 3.9 |
| Prostate Cancer | 2 | 3.9 |
| Adenosquamous Lung Carcinoma | 2 | 3.9 |
| Metastatic Lung Cancer | 2 | 3.9 |
| Metastasis to Bone | 2 | 3.9 |
| Malignant Lung Neoplasm | 2 | 3.9 |
| Lung Squamous Cell carcinoma | 1 | 1.9 |
| Metastatic Pancreatic Carcinoma | 1 | 1.9 |
| Non-Resecable Pancreatic Carcinoma | 1 | 1.9 |
| Colorectal Cancer | 1 | 1.9 |
| Colorectal Cancer Stage II | 1 | 1.9 |
| Metastatic Colon cancer | 1 | 1.9 |
| Non-Resectable Bile Duct Cancer | 1 | 1.9 |
| Breast Cancer Stage IV | 1 | 1.9 |
| Adenosquamous Cell Lung Cancer | 1 | 1.9 |
| Metastatic Fallopian Tube Cancer | 1 | 1.9 |
| Gallbladder Cancer | 1 | 1.9 |
| Gastric Cancer Stage IV, Without Metastasis | 1 | 1.9 |
| Metastatic Breast Cancer | 1 | 1.9 |
| Metastatic Colorectal Cancer | 1 | 1.9 |
| Metastatic Non-Small Cell Lung Cancer | 1 | 1.9 |
| Nodular Sclerosis Hodgkin's Disease | 1 | 1.9 |
| Acute Myeloid Leukemia | 1 | 1.9 |
| B-Cell Lymphoma | 1 | 1.9 |
| Metastasis to Abdominal Cavity | 1 | 1.9 |

| | | |
|---|-----------|-------------|
| Metastasis to Lung | 1 | 1.9 |
| Metastasis to Liver | 1 | 1.9 |
| Mycosis Fungoides Stage IV | 1 | 1.9 |
| Multiple Myeloma | 1 | 1.9 |
| Colon Neoplasm | 1 | 1.9 |
| Neoplasm of the Genitourinary Tract | 1 | 1.9 |
| Malignant Neoplasm of Orbit | 1 | 1.9 |
| Rectal Neoplasm | 1 | 1.9 |
| General Disorders and Administration Site Conditions | 31 | 12.6 |
| Death | 26 | 83.9 |
| Sudden Death | 3 | 9.7 |
| Condition Aggravated | 1 | 3.2 |
| Sudden Cardiac Death | 1 | 3.2 |
| Cardiac Disorders | 33 | 13.4 |
| Acute Myocardial Infarction | 9 | 27.3 |
| Cardiac Failure Congestive | 3 | 9.1 |
| Cardiopulmonary Failure | 3 | 9.1 |
| Cardiac Arrest | 2 | 6.1 |
| Cardiac Failure Chronic | 2 | 6.1 |
| Cardiac Failure | 2 | 6.1 |
| Acute Coronary Syndrome | 2 | 6.1 |
| Atrial Flutter | 1 | 3.0 |
| Unstable Angina | 1 | 3.0 |
| Acute Cor Pulmonale | 1 | 3.0 |
| Electromechanical Dissociation | 1 | 3.0 |
| Aortic Valve Disease | 1 | 3.0 |
| Ventricular Fibrillation | 1 | 3.0 |
| Myocardial Infarction | 1 | 3.0 |
| Myocardial Ischaemia | 1 | 3.0 |
| Cardiorespiratory Arrest | 1 | 3.0 |
| Pericarditis | 1 | 3.0 |
| Nervous System Disorders | 13 | 5.3 |
| Cerebral Haemorrhage | 2 | 15.4 |
| Ischaemic Stroke | 2 | 15.4 |
| Cerebrovascular Accident | 1 | 7.7 |
| Neurodegenerative Disorder | 1 | 7.7 |
| Anoxic Encephalopathy | 1 | 7.7 |
| Amyotrophic Lateral Sclerosis (ALS) | 1 | 7.7 |
| Brain Hematoma | 1 | 7.7 |
| Intracranial Hemorrhage | 1 | 7.7 |

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| Hemorrhagic Stroke | 1 | 7.7 |
| Embolic Cerebral Infarction | 1 | 7.7 |
| Lacunar Infarction | 1 | 7.7 |
| Respiratory, Thoracic, and Mediastinal Disorders | 12 | 4.8 |
| Respiratory Failure | 2 | 16.7 |
| Acute Respiratory Failure | 2 | 16.7 |
| Obliterative Bronchiolitis | 1 | 8.3 |
| Pleural Effusion | 1 | 8.3 |
| Pulmonary Embolism | 1 | 8.3 |
| Interstitial Lung Disease | 1 | 8.3 |
| Pulmonary Fibrosis | 1 | 8.3 |
| Pulmonary Mass | 1 | 8.3 |
| Pneumothorax | 1 | 8.3 |
| Diffuse Panbronchiolitis | 1 | 8.3 |
| Gastrointestinal Disorders | 8 | 3.2 |
| Intestinal Ischaemia | 2 | 25.0 |
| Esophageal Variceal Haemorrhage | 1 | 12.5 |
| Lower Gastrointestinal Haemorrhage | 1 | 12.5 |
| Upper Gastrointestinal Haemorrhage | 1 | 12.5 |
| Bowel Obstruction | 1 | 12.5 |
| Acute Pancreatitis | 1 | 12.5 |
| Duodenal Perforation | 1 | 12.5 |
| Surgical and Medical Procedures | 5 | 2.0 |
| Activation of Macrophages | 1 | 20.0 |
| Radical Neck Dissection | 1 | 20.0 |
| Extended Radical Mastectomy | 1 | 20.0 |
| Coronary Revascularization | 1 | 20.0 |
| Aortic Valve Replacement | 1 | 20.0 |
| Injury, Poisoning, and Procedural Complications | 5 | 2.0 |
| Accident | 1 | 20.0 |
| Procedural Complications | 1 | 20.0 |
| Femoral Neck Fracture | 1 | 20.0 |
| Subdural Hematoma | 1 | 20.0 |
| Insertion Site Reaction | 1 | 20.0 |
| Blood and Lymphatic System Disorders | 3 | 1.2 |
| Bone Marrow Disorders | 1 | 33.3 |
| Bone Marrow Toxicity | 1 | 33.3 |
| Anemia | 1 | 33.3 |
| Hepatobiliary Disorders | 1 | 0.4 |
| Alcoholic Cirrhosis | 1 | 0.5 |

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| Renal and Urinary Disorders | 3 | 1.2 |
| Renal Amyloidosis | 1 | 0.5 |
| Renal Disease | 1 | 0.5 |
| Vascular Disorders | 2 | 0.8 |
| Aortic Aneurysm | 1 | 0.5 |
| Aortic Aneurysm Rupture | 1 | 0.5 |
| Immune System Disorders | 1 | 0.4 |
| Primary Amyloidosis | 1 | 100.0 |
| Psychiatric Disorders | 1 | 0.4 |
| Completed Suicide | 1 | 100.0 |
| Total | 220 | 100.0 |

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Research Unit of the Spanish Society of Rheumatology.
