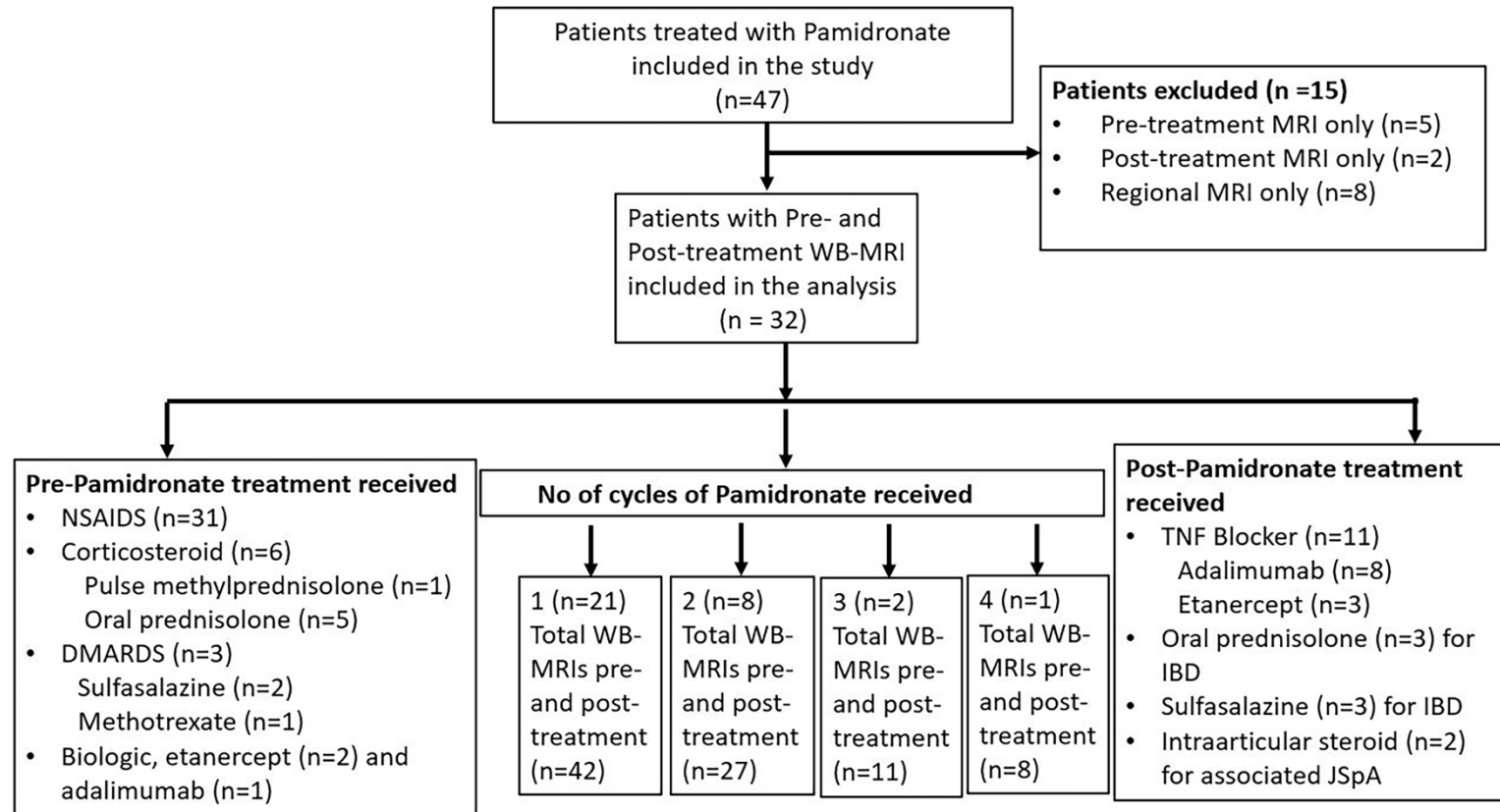


**ONLINE SUPPLEMENTARY MATERIAL**

**Supplementary Figure 1.** Flow diagram shows the case selection process, details of pamidronate cycles and treatment received before and after pamidronate therapy.



DMARD: disease-modifying antirheumatic drug; IBD: inflammatory bowel disease; JSpA: juvenile spondyloarthritis; NSAID: nonsteroidal antiinflammatory drug; TNF: tumor necrosis factor; WB-MRI: whole-body magnetic resonance imaging.

**Supplementary Table 1.** Whole-body MRI scoring system used for quantifying the CNO lesions in this study.

| Whole-Body MRI Scoring System for the CNO Lesions |                   |                        |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |
|---------------------------------------------------|-------------------|------------------------|--------------------------------------------------------------|----------|------------|------------|-------------|-----------------------------------------------------------------------------------------|--------------------------------------------|-------------------------------------------------|-----------------------------------|-------------|----------------|-------------|-----------------------------|-------------|----------------------------------------|-------------|--|--|
| Location                                          |                   |                        | Bone marrow signal size score (involvement of the bone area) |          |            |            |             | Bone marrow signal intensity score (on comparison with adjacent vessel or fluid signal) |                                            |                                                 | Soft tissue high signal intensity |             | Bone expansion |             | Vertebral collapse in spine |             | Posterior element involvement in spine |             |  |  |
|                                                   |                   |                        | None (0)                                                     | <25% (1) | 25-49% (2) | 50-74% (3) | 75-100% (4) | None (0)                                                                                | Less than the adjacent vessel or fluid (1) | Equal or more than adjacent vessel or fluid (2) | None (0)                          | Present (1) | None (0)       | Present (1) | None (0)                    | Present (1) | None (0)                               | Present (1) |  |  |
| Clavicle (R and L)                                |                   |                        |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |
| Scapula (R and L)                                 |                   |                        |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |
| Upper extremity                                   | Humerus (R and L) | Proximal epimetaphysis |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |
|                                                   |                   | Diaphysis              |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |
|                                                   |                   | Distal epimetaphysis   |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |
|                                                   | Radius (R and L)  | Proximal epimetaphysis |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |
|                                                   |                   | Diaphysis              |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |
|                                                   |                   | Distal epimetaphysis   |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |
|                                                   | Ulna (R and L)    | Proximal epimetaphysis |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |
|                                                   |                   | Diaphysis              |                                                              |          |            |            |             |                                                                                         |                                            |                                                 |                                   |             |                |             |                             |             |                                        |             |  |  |





**Supplementary Table 2.** Baseline demographic, clinical, laboratory data, and treatment details from the patients included in this study.

| Characteristic                                                         |                          |
|------------------------------------------------------------------------|--------------------------|
| <b>Demographics (per patient, n= 32)</b>                               |                          |
| Male sex, no. (%)                                                      | 11 (34.37%)              |
|                                                                        | 21 (65.62%)              |
| Mean age at disease onset, years (range)                               | 11.5 (7.3-17)            |
| Mean duration of symptom onset Pre-IV Pamidronate therapy, months      | 31 (4-90)                |
| Family history of autoimmune disease, no. (%)                          | 20 (62.5%)               |
| Positive HLA-B27, no. (%)                                              | 1 (3.12%)                |
| <b>Clinical (per baseline MRI examination, n= up to 32)</b>            |                          |
| Median affected CNO sites count (clinical assessment only), no. (IQR)  | 3 (1.75-4.25)            |
| Localized swelling, no. (%)                                            | 17 (53.12%)              |
| Bone pain, no. (%)                                                     | 32 (100%)                |
| Median baseline VAS score for pain, no. (IQR)                          | 19 (0.7-5.6)             |
| <b>Systemic symptoms, no (%)</b>                                       |                          |
| Fever                                                                  | 1 (3.12%)                |
| Weight loss                                                            | 0                        |
| Fatigue                                                                | 0                        |
| Gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea) | 2 (6.25%)                |
| Rash, no. (%)                                                          | 2 (6.25%)                |
| Enthesitis, no. (%)                                                    | 3 (9.37%)                |
| Uveitis                                                                | 1 (3.12%)                |
| <b>Laboratory (per baseline MRI examination, n=up to 32)</b>           |                          |
| Increased CRP, no. (%)                                                 | 23/32 (71.8%)            |
| Increased ESR, no. (%)                                                 | 21/32 (65.6%)            |
| Increased serum calcium, no. (%)                                       | 5/32 (15.6%)             |
| Increased serum alkaline phosphatase, no. (%)                          | 1/30 (3.3%)              |
| Low serum alkaline phosphatase, no. (%)                                | 6/30 (20%)               |
| Mean baseline serum C-telopeptide (ng/L) (range)                       | 1192.43 (354-2060, n=16) |
| Bone biopsy, no. (%)                                                   | 13 (40.6%)               |
| <b>Treatment details</b>                                               |                          |
| Total no. of cycles of IV Pamidronate, mean (range)                    | 1.46 (1-4)               |
| Total Pamidronate dose (mg) of all cycles, median (IQR)                | 122 (94.25-164)          |
| Cumulative IV Pamidronate Dose (mg/kg/year), median (IQR)              | 2.89 (2.8-2.96)          |

IV = intravenous; CNO = chronic nonbacterial osteomyelitis; IQR = interquartile range; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analogue scale.

**Supplementary Table 3.** Prevalence of CNO lesions on first pre-treatment WB-MRI for all 32 patients.

| Regions assessed on WB-MRI     | Number examined (on first pretreatment MRI) | Bone marrow lesions |       | Bone Expansion | Soft tissue hyperintensity |
|--------------------------------|---------------------------------------------|---------------------|-------|----------------|----------------------------|
| <b>Head</b>                    |                                             |                     |       |                |                            |
| Skull                          | 64                                          | 2                   | 3%    | 0              | 0                          |
| Mandible                       | 64                                          | 4                   | 6%    | 2              | 2                          |
| Total                          | 128                                         | 6                   | 5%    | 2              | 2                          |
| <b>Shoulder girdle</b>         |                                             |                     |       |                |                            |
| Clavicle                       | 64                                          | 9                   | 21.8% | 3              | 4                          |
| Scapula                        | 64                                          | 4                   | 6%    | 0              | 0                          |
| Total                          | 128                                         | 13                  | 10%   | 3              | 4                          |
| <b>Thorax</b>                  |                                             |                     |       |                |                            |
| Sternum                        | 32                                          | 2                   | 6%    | 0              | 0                          |
| Ribs                           | 768                                         | 2                   | 0.3%  | 0              | 0                          |
| Total                          | 800                                         | 4                   | 0.5%  | 0              | 0                          |
| <b>Pelvis</b>                  |                                             |                     |       |                |                            |
| Ilium                          | 64                                          | 5                   | 8%    | 0              | 1                          |
| Sacrum                         | 64                                          | 21                  | 33%   | 1              | 0                          |
| Periacetabulum                 | 64                                          | 11                  | 17%   | 0              | 5                          |
| Ischium/pubis                  | 64                                          | 7                   | 11%   | 0              | 1                          |
| Coccyx                         | 32                                          | 1                   | 3%    | 0              | 0                          |
| Total                          | 288                                         | 45                  | 16%   | 1              | 7                          |
| <b>Upper limb</b>              |                                             |                     |       |                |                            |
| Humerus proximal metaepiphysis | 64                                          | 3                   | 5%    | 0              | 0                          |
| Humerus diaphysis              | 64                                          | 2                   | 3%    | 1              | 1                          |
| Humerus distal metaepiphysis   | 64                                          | 3                   | 5%    | 0              | 0                          |
| Radius proximal metaepiphysis  | 64                                          | 0                   | 0%    | 0              | 0                          |
| Radius diaphysis               | 64                                          | 0                   | 0%    | 0              | 0                          |
| Radius distal metaepiphysis    | 64                                          | 13                  | 20%   | 0              | 0                          |
| Ulna proximal metaepiphysis    | 64                                          | 3                   | 5%    | 0              | 0                          |
| Ulna diaphysis                 | 64                                          | 1                   | 2%    | 0              | 0                          |
| Ulna distal metaepiphysis      | 64                                          | 13                  | 20%   | 0              | 0                          |
| Total                          | 576                                         | 38                  | 7%    | 1              | 1                          |
| <b>Lower limb</b>              |                                             |                     |       |                |                            |
| Femur proximal metaepiphysis   | 64                                          | 12                  | 19%   | 1              | 1                          |
| Femur diaphysis                | 64                                          | 4                   | 6%    | 1              | 2                          |
| Femur distal metaepiphysis     | 64                                          | 32                  | 50%   | 2              | 4                          |
| Tibia proximal metaepiphysis   | 64                                          | 32                  | 50%   | 0              | 3                          |
| Tibia diaphysis                | 64                                          | 3                   | 5%    | 0              | 1                          |
| Tibia distal metaepiphysis     | 64                                          | 42                  | 66%   | 0              | 10                         |
| Fibula proximal metaepiphysis  | 64                                          | 8                   | 13%   | 0              | 0                          |
| Fibula diaphysis               | 64                                          | 0                   | 0%    | 0              | 0                          |
| Fibula distal metaepiphysis    | 64                                          | 20                  | 31%   | 0              | 5                          |
| Patella                        | 64                                          | 2                   | 3%    | 0              | 0                          |
| Total                          | 640                                         | 155                 | 24%   | 4              | 26                         |

| <b>Spine</b> | Number Examined | Marrow regions involved |      | Collapse | Soft tissue high signal | Posterior Element |
|--------------|-----------------|-------------------------|------|----------|-------------------------|-------------------|
| cervical     | 224             | 2                       | 1%   | 1        | 0                       | 2                 |
| Thoracic     | 384             | 9                       | 2%   | 3        | 1                       | 0                 |
| Lumbar       | 160             | 7                       | 4%   | 1        | 1                       | 0                 |
| Total        | 768             | 18                      | 2%   | 5        | 2                       | 2                 |
|              |                 | Involvement             |      |          |                         |                   |
| <b>Hands</b> | 64x27=1728      | 11                      | 0.6% |          |                         |                   |
| <b>Feet</b>  | 64x26=1664      | 97                      | 6%   |          |                         |                   |
| Total        | 3392            | 108                     | 3%   |          |                         |                   |

**Supplementary Table 4.** Treatment response of WB-MRI lesions to pamidronate.

| Number of cycles | Number of patients included in those cycles (n) | Lesions ( $\geq 1$ ) on pre-treatment MRI (n) | Lesions resolved ( $\geq 1$ to $< 1$ ) (% of pretreatment lesions) | Lesions persisted ( $\geq 1$ to $\geq 1$ ) (includes partly improved, stable and worsened lesions) | Lesions worsened (post $>$ pre, not including new) (% of pretreatment lesions) | New lesions ( $< 1$ to $> 1$ ) (% of pretreatment lesions) | Lesions ( $\geq 1$ ) on post-treatment MRI (n) |
|------------------|-------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------|------------------------------------------------|
| 1                | 32                                              | 279                                           | 96 (34)                                                            | 183                                                                                                | 21 (7.5)                                                                       | 46 (16.4)                                                  | 229                                            |
| 2                | 11                                              | 94                                            | 71 (76)                                                            | 23                                                                                                 | 2 (2)                                                                          | 14 (14.9)                                                  | 37                                             |
| 3                | 3                                               | 16                                            | 8 (50)                                                             | 8                                                                                                  | 0                                                                              | 4                                                          | 12                                             |
| 4                | 1                                               | 13                                            | 9 (69)                                                             | 4                                                                                                  | 0                                                                              | 1                                                          | 5                                              |

This frequency table does not include hands and feet bone lesions, because the hand and feet lesions were not tracked per lesion over time in contrast to the remainder.