Treatment of adult-onset Still's disease

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Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Apr 2024. | **This topic last updated:** Sep 11, 2023.

INTRODUCTION — Adult-onset Still's disease (AOSD) is an inflammatory disorder characterized by quotidian (daily) fevers, arthritis, and an evanescent rash. The disease can have a monophasic, intermittent, or chronic course.

Following its initial description in children by George Still in 1896, "Still's disease" became the eponymous term for all childhood-onset arthritis, subsequently restricted to the febrile form now termed systemic juvenile idiopathic arthritis (sJIA) [1,2]. In 1971, Bywaters described a series of adult patients with a syndrome that closely resembled sJIA [3]. "Adult-onset Still's disease" is now the most widely used term for the condition when it begins after the patient's 16th birthday. AOSD and sJIA are increasingly recognized as belonging to the same clinical continuum [4]. (See "Systemic juvenile idiopathic arthritis: Clinical manifestations and diagnosis".)

The treatment and prognosis of AOSD will be reviewed here. The clinical manifestations and diagnosis of AOSD and the treatment of sJIA are presented separately. (See "Clinical manifestations and diagnosis of adult-onset Still's disease" and "Systemic juvenile idiopathic arthritis: Treatment".)

GOALS OF THERAPY — The goals of therapy include:

- Control of the physical signs and symptoms of inflammation (eg, fever, rash, morning stiffness, joint pain, and swelling) and, secondarily, control of laboratory indices of inflammation (eg, elevations in the erythrocyte sedimentation rate [ESR] and levels of C-reactive protein [CRP]). (See "Clinical manifestations and diagnosis of adult-onset Still's disease", section on 'Clinical presentation'.)
- Prompt recognition and treatment of a hyperinflammatory complication of adult-onset Still's disease (AOSD) termed macrophage activation syndrome (MAS). (See "Systemic juvenile idiopathic arthritis: Course, prognosis, and

complications", section on 'Macrophage activation syndrome' and "Systemic juvenile idiopathic arthritis: Treatment", section on 'Macrophage activation syndrome' and "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis" and "Treatment and prognosis of hemophagocytic lymphohistiocytosis", section on 'MAS/Rheumatologic conditions' and "Systemic juvenile idiopathic arthritis: Treatment".)

Initiation of many treatments has been associated temporally with the appearance or worsening of MAS [5-9]. Such reports may simply reflect inadequate treatment of subclinical MAS but highlight the need for close observation of patients with AOSD beginning treatment, including screening laboratory tests for MAS within two weeks of any substantial changes in therapy. (See 'Monitoring for MAS' below.)

- Prevention of end-organ damage, including joint injury and other major organ complications. (See "Clinical manifestations and diagnosis of adult-onset Still's disease", section on 'Clinical presentation'.)
- Minimization of the risk of adverse effects of therapy, including long-term effects of glucocorticoids. (See "Major adverse effects of systemic glucocorticoids".)

PRETREATMENT EVALUATION AND PREVENTION OF ADVERSE DRUG EFFECTS

- **Confirmation of the diagnosis** – It is important to exclude other systemic conditions that may present with symptoms similar to adult-onset Still's disease (AOSD), such as infection and malignancy, before initiating immunosuppressive therapies. Where uncertainty remains, initiation of treatment with an interleukin (IL) 1 antagonist rather than glucocorticoids can provide important diagnostic information (see 'Anakinra: Efficacy and rationale' below). The diagnosis and differential diagnosis of AOSD are described in detail separately. (See "Clinical manifestations and diagnosis of adult-onset Still's disease".)
- **Pretreatment testing** – The baseline testing, screening, and preventive interventions generally performed prior to initiating therapy with any nonbiologic, targeted synthetic (small molecule), or biologic disease-modifying antirheumatic drug (DMARD), and glucocorticoids are generally the same as those used for rheumatoid arthritis (RA); these are described in detail separately (see "General principles and overview of management of rheumatoid arthritis in adults", section on 'Pretreatment evaluation' and "Interleukin 1 inhibitors: Biology, principles of use, and adverse events", section on 'Pretreatment testing'). Briefly, these include:
  - **General testing for all patients** – Baseline complete blood count (CBC), serum creatinine, aminotransferases, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). In patients receiving IL-6 inhibitors and Janus kinase (JAK) inhibitors, lipids are also monitored. In AOSD, to assess for the presence of macrophage activation syndrome (MAS), we also assess ferritin and D-dimer.

- **Hepatitis virus screening** – In all patients without serologically confirmed hepatitis, we screen for hepatitis B and C before initiating therapy with conventional DMARDs, including methotrexate (MTX) and leflunomide (LEF); biologic DMARDs; and JAK inhibitors.

- **Testing for latent tuberculosis** – We screen for latent tuberculosis (TB) with an interferon-gamma release assay or with skin testing prior to all biologic DMARDs and prior to use of a JAK inhibitor.

  We obtain a chest radiograph in patients with a history of other risk factors for latent TB, even if screening tests are negative, given the risks of false-negative testing. Additionally, screening should be repeated in patients with new TB exposures. Glucocorticoids and other factors may cause false-negative results. Screening for latent TB is discussed in detail separately. (See "Risk of mycobacterial infection associated with biologic agents and JAK inhibitors" and "Tuberculosis infection (latent tuberculosis) in adults: Approach to diagnosis (screening)".)

It is not always necessary to await completion of screening for latent TB before beginning short-term IL-1 inhibition with anakinra, particularly when it is urgent to initiate such treatment since IL-1 inhibition does not pose a demonstrated risk for TB reactivation. (See 'Approach to initial therapy' below and "Interleukin 1 inhibitors: Biology, principles of use, and adverse events", section on 'Infection'.)

- **Immunization** – The approach to immunization is generally the same as in patients with RA and other autoimmune rheumatic diseases. To the extent possible, patients should receive vaccines at appropriate intervals prior to the start of immunosuppressive drug therapy, although this may not always be feasible. Vaccines should not be given until febrile episodes are controlled. Immunization in patients with rheumatic diseases is described in detail separately. (See "Immunizations in autoimmune inflammatory rheumatic disease in adults".)

- **Antibiotic prophylaxis** – There is uncertainty regarding which patients with AOSD, based upon their respective treatment regimens and medication doses, are likely to benefit from the additional use of prophylactic antibiotics to prevent *Pneumocystis* pneumonia. Generally, patients being treated with prednisone (or equivalent) in a dose of at least 20 mg daily for greater than a month, especially if in combination with another immunosuppressive medication, are among those most likely to benefit from prophylactic treatment. (See "Treatment and prevention of Pneumocystis pneumonia in patients without HIV", section on 'Indications' and "Treatment and prevention of Pneumocystis pneumonia in patients without HIV", section on 'Regimens'.)

INITIAL THERAPY: NEW-ONSET DISEASE

Approach to initial therapy — Therapeutic decisions in newly diagnosed adult-onset Still's disease (AOSD) are based upon whether macrophage activation syndrome (MAS), a "cytokine storm" that can be life threatening, is present or

suspected, and by the severity of disease; it may be influenced by whether systemic or arthritic features are predominant. During periods of active systemic disease, patients are at highest risk of developing MAS. (See "Clinical manifestations and diagnosis of adult-onset Still's disease".)

Arthritis may be evident early in disease or appear subsequently and often persists after systemic symptoms have resolved. In new-onset disease, severe or highly symptomatic arthritis can be an important target of therapy. Treatment of established AOSD may differ from new-onset disease. (See 'Subsequent therapy: Established disease' below.)

We address the following clinical questions before starting therapy:

- **Is MAS present?** – The first priority in new-onset AOSD is to exclude incipient or active MAS requiring immediate intervention. Criteria developed for the diagnosis of MAS in systemic juvenile idiopathic arthritis (sJIA) [10] have been applied but not extensively tested in patients with AOSD [11]. The diagnosis of MAS in AOSD and in sJIA is described in detail separately. (See 'Concern for incipient or active MAS' below and 'Monitoring for MAS' below and "Clinical manifestations and diagnosis of adult-onset Still's disease", section on 'Macrophage activation syndrome' and "Systemic juvenile idiopathic arthritis: Course, prognosis, and complications", section on 'Macrophage activation syndrome'.)

  The treatment of MAS, including in patients with rheumatic disease such as AOSD, is also described separately. (See "Treatment and prognosis of hemophagocytic lymphohistiocytosis", section on 'MAS/Rheumatologic conditions'.)

  The management of AOSD in patients with a high degree of suspicion of concomitant or incipient MAS frequently involves the use of combination therapy with a biologic, such as anakinra, together with glucocorticoids. (See 'Concern for incipient or active MAS' below.)

- **Is disease mild to moderate or moderate to severe?** – For patients without evidence of active or incipient MAS, a distinction should be made between patients with mild or mild to moderate disease, who may initially be treated with nonsteroidal antiinflammatory drugs (NSAIDs), and patients with moderate to severe disease, who require treatment with a biologic agent, usually anakinra or another interleukin (IL) 1 inhibitor, glucocorticoids, or combination therapy. (See 'Mild to moderate disease' below and 'Moderate to severe disease' below.)

  - **Mild to moderate** – Mild to moderate disease at disease onset is characterized by nondisabling fever, rash, arthralgias or mild arthritis, and the absence of MAS.

  - **Moderate to severe** – Moderate to severe disease may be defined by the additional presence of clinically significant serositis (eg, pleurisy or peritonitis), moderate to severe and debilitating polyarthritis, persistent high fevers despite treatment with NSAIDs, or internal organ involvement. (See "Clinical manifestations and diagnosis of adult-onset

Still's disease", section on 'Clinical presentation'.)

There are no reliable prognostic criteria in new-onset AOSD to discriminate patients who will have a mild, self-limited course from those who will have a more severe chronic course [12]. For this reason, we do not base our decision to use or withhold biologic therapy on particular clinical features at presentation, and generally initiate a disease-modifying antirheumatic drug (DMARD) if symptoms are not completely controlled after two weeks of NSAIDs. In patients with severe or highly symptomatic disease, we frequently begin biologic therapy as soon as possible, beginning with a combination of biologics and glucocorticoids if incipient or early MAS is suspected.

Direct evidence regarding the efficacy of different treatment strategies for new-onset AOSD is derived from observational case series and from clinical experience, both in AOSD and in sJIA.

Mild to moderate disease — For patients suspected of new-onset AOSD with no more than mild to moderate symptoms (see 'Approach to initial therapy' above), and in the absence of MAS, we suggest initial management with NSAIDs alone, rather than glucocorticoids, DMARDs, or biologics, especially while evaluation for alternate causes of fever (eg, infection or lymphoma) is ongoing. An antiinflammatory dose and regimen of NSAIDs should be used; typical choices include naproxen (500 mg twice daily), ibuprofen (800 mg three times daily), and indomethacin (25 to 50 mg three times daily). There is no evidence that any one NSAID has greater efficacy for AOSD than another.

Up to 20 percent of patients achieve control of the signs and symptoms of mild AOSD with NSAIDs [3,5,13-15]. However, NSAIDs are often insufficient, and in many patients, fevers, rash, and joint symptoms become or remain intolerable despite the use of NSAIDs or more severe features develop necessitating additional intervention. The approach for patients who have not responded sufficiently to a 7- to 14-day trial of an NSAID alone during the acute phase of the illness is similar to that for patients who present with moderate to severe disease. (See 'Moderate to severe disease' below.)

Most patients in whom NSAIDs alone are inadequate to control symptoms should discontinue NSAIDs as soon as possible after they are switched to glucocorticoids. Patients receiving NSAIDs together with glucocorticoids should receive prophylactic therapy for the prevention of NSAID gastropathy. (See "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity".)

The adverse effects of NSAIDs are generally the same as in other conditions and are described in detail separately (see "Nonselective NSAIDs: Overview of adverse effects" and "Overview of COX-2 selective NSAIDs", section on 'Toxicities and possible toxicities'). Underlying cardiovascular and gastrointestinal risk factors should be considered during NSAID initiation but are not absolute contraindications as there are limited effective options for initial AOSD therapy. (See "NSAIDs: Adverse cardiovascular effects" and "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity" and "NSAIDs (including aspirin): Treatment and secondary prevention of gastroduodenal toxicity".)

Salicylates, historically a mainstay of therapy for sJIA, are now seldom used to treat either AOSD or sJIA because their therapeutic index is narrower than that of most nonsalicylate NSAIDs.

In patients unable to tolerate NSAIDs, glucocorticoids in low to moderate doses (eg, prednisone 10 to 30 mg orally once daily or equivalent) can be an effective alternative. However, since glucocorticoid monotherapy tends to become prolonged, we prefer in such cases to advance rapidly to a biologic DMARD, in order to discontinue glucocorticoids within two months. For patients primarily with arthritis rather than systemic symptoms, methotrexate (MTX) is a reasonable alternative to a biologic DMARD as the initial glucocorticoid-sparing agent. (See 'Glucocorticoid-sparing therapy for chronic management' below.)

Moderate to severe disease

Treatment approach — For patients with new-onset moderate to severe AOSD and those with milder disease in whom NSAIDs are inadequate, we prefer to initiate therapy with anakinra. Glucocorticoids are a reasonable alternative but have some comparative disadvantages in this setting. (See 'Anakinra: Efficacy and rationale' below and 'Glucocorticoids: Efficacy and rationale' below.)

- Anakinra – For management of new-onset moderate to severe AOSD (see 'Approach to initial therapy' above) and for patients in whom two weeks of NSAIDs are insufficient (see 'Mild to moderate disease' above), we suggest anakinra rather than continued NSAIDs alone, glucocorticoids, or another DMARD (such as biologics and conventional synthetic DMARDs). Our usual initial dose is 100 mg subcutaneously daily. For patients in whom a partial response is observed after 7 to 14 days, the dose can be increased to 100 mg twice daily. (See 'Anakinra: Efficacy and rationale' below.)

  For patients who have attained remission, spacing of anakinra injections to every other day and then every third day provides an opportunity to test whether the underlying disease is truly in remission, facilitating discontinuation of therapy. The duration of remission required to optimize the probability of sustained remission is unknown; a three-month period of remission is reasonable [16].

  Given greater concerns about exacerbating bacterial infections with IL-6 blockade than with IL-1 blockade, and the much longer half-lives of the IL-6 inhibitors tocilizumab or sarilumab (approximately 8 to 14 days) than anakinra (six hours), we prefer anakinra in this setting and typically do not employ tocilizumab or sarilumab in new-onset disease where diagnostic uncertainty remains, as is often the case.

- **Glucocorticoids** – Glucocorticoids are a reasonable alternative to anakinra, particularly for patients unable to obtain anakinra. Initial doses of prednisone for AOSD range from 20 to 60 mg orally daily, depending upon an individualized assessment of the severity of disease and the rapidity of the initial response to therapy. (See 'Glucocorticoids: Efficacy and rationale' below.)

  Oral glucocorticoids treat both systemic and arthritic features of AOSD.

Patients usually respond to glucocorticoids within hours to a few days, but a longer period of therapy may be required in some patients [5,14]. Approximately 70 percent of patients respond to glucocorticoids alone or to glucocorticoids used after a trial of NSAIDs [13,17].

Some patients with monoarthritis or oligoarthritis and those with very severe or refractory disease may benefit from intraarticular or intravenous glucocorticoid administration, respectively:

- Intraarticular glucocorticoids – Patients with one or two inflamed joints despite use of systemic medications may benefit from intraarticular glucocorticoid injections. In such cases, consideration should always be given to the possibility of an alternate cause of arthritis, such as bacterial infection or Lyme disease, which may be assessed by additional studies such as synovial fluid Gram stain and culture and Lyme serology, respectively. (See "Use of glucocorticoids in the treatment of rheumatoid arthritis", section on 'Intraarticular therapy' and "Musculoskeletal manifestations of Lyme disease" and "Septic arthritis in adults" and "Diagnosis of Lyme disease".)

- Intravenous glucocorticoids – Pulse intravenous methylprednisolone, 1000 mg daily for one to three days, is typically reserved for patients with MAS but represents an option for patients with otherwise refractory systemic or arthritic disease [18,19].

Once control of symptoms is achieved for at least two weeks and laboratory indices have normalized, glucocorticoids are tapered rapidly to a low-maintenance dose for two to three months to maintain control of signs and symptoms of disease. As an example, in a patient initially receiving 60 mg of prednisone daily, we may decrease the daily dose of glucocorticoids every week with the aim of reducing prednisone dosing to below 10 mg daily within eight weeks, then discontinuing glucocorticoid therapy over the subsequent three months. Since only a relatively small proportion of patients with AOSD will achieve sustained remission with glucocorticoids alone, we generally initiate traditional or biologic DMARD therapy in patients requiring prednisone 10 mg daily or more for greater than one month. Our long-term goal is complete discontinuation of glucocorticoids, although some patients may continue to require up to 5 mg daily. (See 'Subsequent therapy: Established disease' below and "Use of glucocorticoids in the treatment of rheumatoid arthritis" and "Glucocorticoid withdrawal".)

Anakinra: Efficacy and rationale — Initiating treatment with the IL-1 antagonist anakinra as monotherapy may be effective in AOSD, especially early in disease, and avoid serious adverse effects that are often associated with the use of glucocorticoids. Anakinra is a recombinant human IL-1 receptor antagonist and represents our preferred first-line biologic therapy for AOSD because of its efficacy, short half-life (six hours), and easy titratability, on the basis primarily of data accumulated within new-onset sJIA [16,20-22]. (See "Systemic juvenile idiopathic arthritis: Treatment", section on 'Anakinra' and "Systemic juvenile idiopathic arthritis: Course, prognosis, and complications".)

While not all patients with AOSD respond to anakinra, absence of any reduction in fever and rash is sufficiently uncommon to justify careful reconsideration of the diagnosis. Importantly, since anakinra is not typically associated with reactivation of tuberculosis (TB) infection and exhibits a favorable safety profile as monotherapy even in serious bacterial infection, if clinically necessary, anakinra can be part of the diagnostic and therapeutic evaluation for AOSD even before occult infection has been fully excluded [23,24]. By contrast, a response to glucocorticoids is nonspecific and may complicate the ongoing search for alternate underlying diagnoses, such as lymphoproliferative malignancy. The mechanism of action and adverse effects of anakinra and other IL-1 inhibitors are described in detail separately. (See "Interleukin 1 inhibitors: Biology, principles of use, and adverse events".)

Much of the support for initiating therapy with anakinra in AOSD has been extrapolated from the experience in patients with sJIA, in whom a substantial response to anakinra monotherapy is observed in approximately 70 to 90 percent of patients; the response to anakinra in AOSD appears comparable [25,26]. (See "Systemic juvenile idiopathic arthritis: Treatment", section on 'Anakinra'.)

Some evidence also indicates that incorporating anakinra into initial therapy could help to reduce the subsequent development of chronic arthritis, despite the relatively modest efficacy of anakinra in rheumatoid arthritis (RA) in adults [12,20]. More extensive investigation is needed to determine whether there is in fact a "window of opportunity" in sJIA/AOSD during which early effective intervention might alter the natural history of disease, although this possibility is now supported by correlative observational and experimental evidence [12,22,27-29].

Glucocorticoids: Efficacy and rationale — Glucocorticoids are an alternative to anakinra and an acceptable first option in patients with AOSD who remain symptomatic after 7 to 14 days of NSAIDs. Glucocorticoids are rapidly effective, simple to titrate, and inexpensive. However, we generally prefer anakinra if available to minimize short- and long-term exposure to glucocorticoids. (See 'Moderate to severe disease' above and 'Anakinra: Efficacy and rationale' above.)

Higher initial doses (equivalent to prednisone 0.8 to 1 mg/kg daily) may be preferable to lower doses when glucocorticoids are used as initial therapy, but even with higher doses the disease fails to respond completely in many patients, and effective therapy often requires a prolonged treatment course. This was illustrated in a retrospective series that compared 40 patients with AOSD treated with low-dose glucocorticoids (0.2 to 0.3 mg/kg daily) with 40 patients treated with high-dose glucocorticoids (0.8 to 1 mg/kg daily); the doses used were based upon the clinical judgment of the treating clinicians [30]. Remission rates after six months were lower in the low-dose group (25 versus 65 percent), and glucocorticoid therapy could be discontinued by 18 months in fewer of the patients treated with low-dose therapy (9 versus 34 percent). These findings are similar to those of an observational series in sJIA, where conventional (nonbiologic) treatment was associated with ongoing glucocorticoid therapy six months after diagnosis in nearly 70 percent of children [31].

Additionally, in a study of 45 patients with AOSD, among whom there were 56 trials of glucocorticoid therapy, those with the chronic articular pattern of disease were less likely to respond than were patients with AOSD with systemic disease but without chronic articular involvement (7 of 20 [35 percent] versus 28 of 36 [78 percent]) [13].

In patients treated with systemic glucocorticoids, appropriate preventive measures to minimize impact on bone health and to prevent other adverse effects of glucocorticoids should be pursued. The prevention of bone loss and the major side effects of systemic glucocorticoid use are described separately. (See "Prevention and treatment of glucocorticoid-induced osteoporosis" and "Major adverse effects of systemic glucocorticoids".)

Concern for incipient or active MAS — In patients with new-onset AOSD where incipient or active MAS remains a concern, we typically combine anakinra with glucocorticoid therapy. Concern for MAS is particularly high in patients with elevation in ferritin levels out of proportion to other inflammatory markers, transaminase elevation, marked elevation in D-dimer, thrombocytopenia, and/or a decreasing erythrocyte sedimentation rate (ESR) despite continued elevation of C-reactive protein (CRP). In hospitalized patients, we frequently employ anakinra in high doses (up to 100 mg four times daily, potentially via the intravenous route [32]) as well as pulse-dose intravenous glucocorticoids (methylprednisolone 1000 mg intravenously daily for one to three days). The clinical manifestations, diagnosis, and management of MAS are described separately. (See "Clinical manifestations and diagnosis of adult-onset Still's disease", section on 'Macrophage activation syndrome' and "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis", section on 'Rheumatologic disorders/MAS' and "Treatment and prognosis of hemophagocytic lymphohistiocytosis" and "Treatment and prognosis of hemophagocytic lymphohistiocytosis", section on 'MAS/Rheumatologic conditions'.)

SUBSEQUENT THERAPY: ESTABLISHED DISEASE

Treatment approach — The specific drug choices for subsequent management of adult-onset Still's disease (AOSD) after initial treatment of new disease depend upon the effectiveness and risks of first-line therapies and the range and severity of disease manifestations.

Treatment decisions are based upon the same general principles as in new-onset disease (ie, control of inflammation, prevention of end-organ damage, adverse effects of medications [especially glucocorticoids], and rapid recognition and intervention for macrophage activation syndrome [MAS]) (see 'Goals of therapy' above). As with new-onset disease, evidence for specific treatments in AOSD is principally available as case series, in some cases supplemented by small clinical trials. Treatment depends upon the prior response to therapy and clinical features:

- **Good response to initial therapy** – In patients who respond to initial management of AOSD, the key priority is minimization of glucocorticoid exposure if present. Achieving discontinuation of glucocorticoids may require optimization of dosing, for example, by an adjustment in the dose or

frequency of a biologic agent or the dose or route of administration of methotrexate (MTX).

For patients who have attained complete remission off glucocorticoids, including resolution of clinical symptoms and normalization of laboratory values, we typically maintain the disease-modifying antirheumatic drug (DMARD) regimen for three to six months before we consider drug tapering, beginning with the agent of greatest concern with respect to side effects. (See 'Medication tapering and duration of therapy' below.)

- **Mild systemic and/or articular disease** – Nonsteroidal antiinflammatory drugs (NSAIDs) can provide relief for mild systemic and arthritic features of AOSD. Although they are particularly useful in the initial treatment of mild to moderate disease, we also use NSAIDs in a limited fashion for several days to weeks on an as-needed basis as an antiinflammatory adjunctive therapy in patients with established or chronic disease [5,13-16]. The use of NSAIDs in AOSD is described in more detail elsewhere in this topic review (see 'Mild to moderate disease' above). Patients receiving NSAIDs together with glucocorticoids should receive prophylactic therapy for the prevention of NSAID gastropathy; prophylaxis should also be considered for all patients on chronic NSAIDs after review of individual risk factors. (See "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity".)

- **Moderate to severe disease requiring chronic glucocorticoid therapy** – Patients unable to taper glucocorticoids to ≤10 mg daily of prednisone (or equivalent) or who have evidence of joint injury require additional therapy, usually with a conventional synthetic DMARD, a biologic DMARD, or both, to control disease and limit or prevent adverse effects of chronic glucocorticoid therapy. (See 'Glucocorticoid-sparing therapy for chronic management' below.)

Glucocorticoid-sparing therapy for chronic management — For patients unable to reduce glucocorticoids to ≤10 mg daily of prednisone (or equivalent) we suggest the addition of a glucocorticoid-sparing DMARD rather than continuing the same level of glucocorticoid therapy. For patients with arthritis, and patients with evidence of erosive joint disease on joint radiographs, we prefer methotrexate (MTX); for patients with predominantly systemic symptoms and/or suspected incipient MAS, we prefer anakinra, an interleukin (IL) 1 inhibitor. (See 'Methotrexate and other conventional DMARDs' below and 'Anakinra' below.)

Alternatives to MTX include leflunomide (LEF), another conventional synthetic DMARD, and tocilizumab or another IL-6 inhibitor (see 'Methotrexate and other conventional DMARDs' below and 'Interleukin 6 inhibition' below). We tend to prefer IL-6 blockade to IL-1 blockade in a patient with AOSD in whom arthritis is the major clinical feature. By contrast, evidence that high-dose anakinra can be effective in MAS leads us to prefer IL-1 blockade in patients at high risk for this complication [20,33], and IL-1 inhibition also remains an option for patients with arthritis who are resistant to MTX and to an IL-6 inhibitor. Canakinumab, a longer-acting IL-1 inhibitor than anakinra, may also be effective in some patients

with arthritis, and we prefer it over anakinra for chronic therapy in patients with arthritis who need an IL-1 inhibitor because of its requirement for monthly rather than daily injection. (See 'Canakinumab and rilonacept' below.)

For patients with arthritis that has not responded to conventional DMARDs (MTX or LEF) after 8 to 12 weeks, we add an IL-6 inhibitor, or alternatively an IL-1 inhibitor. For those who are refractory to IL-1 and IL-6 blockade, a tumor necrosis factor (TNF) inhibitor, usually infliximab, may be used, but we restrict its use to this setting because of the relative inefficacy of TNF blockade for systemic manifestations of AOSD. (See 'Tumor necrosis factor inhibitors' below.)

For patients with systemic disease who are unable to obtain anakinra or who are intolerant of daily injections, the IL-1 inhibitor canakinumab (or potentially rilonacept) is a reasonable alternative, followed by tocilizumab. Sarilumab, another IL-6 inhibitor, could be considered as a third-line agent as well [34]. (See 'Canakinumab and rilonacept' below and 'Interleukin 6 inhibition' below.)

Therapeutic agents

Methotrexate and other conventional DMARDs

- **Dosing and administration** – Methotrexate (MTX) is given on a once-weekly basis using the same approach as in adult rheumatoid arthritis (RA). We typically initiate MTX at a dose between 10 to 15 mg once weekly for most patients, escalating as tolerated after four weeks to 20 to 25 mg weekly. Split-dose oral therapy and subcutaneous injection can enhance absorption in case of partial responses, as absorption may not be commensurate with dose increases in patients receiving ≥15 mg, in some cases also helping to overcome gastrointestinal intolerance. Concomitant folic acid or folinic acid is also taken, which helps to minimize adverse events. (See "Initial treatment of rheumatoid arthritis in adults" and "Use of methotrexate in the treatment of rheumatoid arthritis".)

- **Efficacy of** methotrexate – Generally regarded as less effective for the systemic manifestations of AOSD, including MAS, MTX can help to address arthritic manifestations as reflected in its utilization in approximately half of patients with AOSD [13,35,36]. Limited data from observational studies suggest that MTX is an effective glucocorticoid-sparing agent, enabling patients to taper or discontinue glucocorticoids and providing some improvement in systemic symptoms [37,38]. The only randomized controlled trial of MTX was performed in 45 patients with systemic juvenile idiopathic arthritis (sJIA), finding nonsignificant improvement in joint features and no change in systemic features, though combined analysis with other forms of JIA within the same trial suggested modest improvement in arthritis severity [39].

- **Alternatives to** methotrexate – For patients in whom MTX is poorly tolerated or ineffective, other conventional DMARDs may also be employed, although data for efficacy remain scant. In our experience, LEF (10 to 20 mg daily) can be a helpful adjunct in AOSD patients with arthritis who cannot tolerate full-dose MTX or in whom MTX is insufficiently effective [40,41].

Combined MTX/LEF therapy can be effective but requires particular vigilance with respect to monitoring for hepatotoxicity [42,43]. The approach to using LEF is generally the same as in RA. (See "Pharmacology, dosing, and adverse effects of leflunomide in the treatment of rheumatoid arthritis" and "Alternatives to methotrexate for the initial treatment of rheumatoid arthritis in adults", section on 'Leflunomide'.)

Hydroxychloroquine (HCQ) and sulfasalazine (SSZ), common DMARDs in RA, do not appear to have a routine role in the treatment of AOSD. HCQ therapy is often reported in series of AOSD, but to our knowledge, no efficacy data are available, and we do not regularly use it for this indication [13,35,36]. SSZ is anecdotally associated with an unusually high rate of adverse events in AOSD, including provocation of MAS, and is typically avoided [6,14].

Interleukin 1 blockade

Anakinra — Anakinra is most effective for patients with AOSD when used as treatment of new-onset disease (see 'Anakinra: Efficacy and rationale' above) but also shows substantial benefit for chronic disease, as shown best in patients with sJIA (see "Systemic juvenile idiopathic arthritis: Treatment" and "Systemic juvenile idiopathic arthritis: Treatment", section on 'Interleukin 1 inhibitors'). Observational data suggest that the efficacy of anakinra in AOSD is similar to that in sJIA [25,26]. Case series report utility in AOSD that has been refractory to treatment with other medications, including glucocorticoids, MTX, other traditional (nonbiologic) DMARDs, and TNF inhibitors [13,44-49]. Anakinra 100 mg administered by daily subcutaneous injection is the typical dosing for patients with chronic AOSD, although escalation to twice-daily dosing is necessary in some patients.

The response to anakinra in patients with AOSD is illustrated by the following examples:

- In a randomized, open-label trial of 22 patients with AOSD whose disease was not responsive to glucocorticoids with or without a traditional DMARD, administration of anakinra (100 mg administered subcutaneously daily) resulted in remission in 6 of 12 patients, compared with only 2 of 10 receiving a nonbiologic DMARD (MTX, azathioprine, or LEF) [46]. Three patients receiving anakinra, but none receiving DMARDs alone, were able to discontinue glucocorticoids.

- A retrospective nationwide French survey identified 28 patients with AOSD resistant to NSAIDs, glucocorticoids, and prior DMARDs (including 14 who had not responded adequately to biologic agents) who were treated with anakinra (100 mg administered by daily subcutaneous injection) alone or together with MTX. All patients responded to therapy, and patients were able to reduce glucocorticoid doses [49]. After a mean follow-up of 23 months, 16 patients (57 percent) experienced complete remission, and three of these patients could discontinue anakinra. Eight patients (29 percent) had a partial response and four patients (14 percent) had a period of complete remission but then experienced loss of efficacy. Dose tapering or discontinuation was associated with relapse in half of the patients. Two

patients discontinued anakinra because of intensely pruritic rashes at the injection site, and two with inadequate responses discontinued the medication.

Canakinumab and rilonacept — The IL-1 inhibitors canakinumab and rilonacept can be effective in patients with AOSD [25,45,50,51]. Unlike anakinra, canakinumab (an anti-IL-1 beta monoclonal antibody) is approved for AOSD by the US Food and Drug Administration, helping to facilitate access, and is administered by monthly subcutaneous injection. For these reasons, it is appealing for patients who are unable to obtain anakinra or intolerant of daily injections [52]. Canakinumab has been employed as the first biologic in some patients with AOSD, although use as first-line therapy before patients have failed other treatments has not been reported [50-53].

A randomized trial of canakinumab in 36 patients with AOSD revealed results consistent with efficacy data in sJIA, although in this small study the formal endpoint was not met [52]. Canakinumab is dosed at 4 mg/kg, maximum 300 mg, by subcutaneous route every four weeks [52]. Canakinumab can be effective in patients in whom treatment with anakinra was unsuccessful [50]. Although supported by fewer data, rilonacept (an IL-1 trap molecule that is a soluble dimeric fusion protein) may be an alternative for patients in whom both anakinra and canakinumab have failed [54]. (See "Systemic juvenile idiopathic arthritis: Treatment", section on 'Interleukin 1 inhibitors'.)

Interleukin 6 inhibition — Tocilizumab (a blocking antibody directed at the IL-6 receptor) is employed in AOSD and sJIA at doses typically higher than those used in RA. Clinical trials employed doses of 8 mg/kg intravenously every two weeks [55,56]. In practice, for reasons of convenience, we often begin with tocilizumab using the subcutaneous route, 162 mg weekly, although intravenous dosing and dose escalation can be helpful in some patients who fail to respond fully. A role for IL-6 in sJIA was defined in the 1990s and confirmed through a randomized trial of the IL-6 receptor antagonist tocilizumab in 2012, showing responses both for systemic and arthritic features [55,57,58]. The use and adverse effects of tocilizumab are described in further detail separately. (See "Treatment of rheumatoid arthritis in adults resistant to initial conventional synthetic (nonbiologic) DMARD therapy", section on 'Methotrexate plus IL-6 inhibitor/IL-6 inhibitor monotherapy' and "Treatment of rheumatoid arthritis in adults resistant to initial biologic DMARD therapy", section on 'IL-6 inhibitor therapies'.)

The benefits of tocilizumab in AOSD have been shown in case series and a small randomized trial [59-63]. The findings are illustrated by the following reports:

- The efficacy and safety of tocilizumab were examined in a randomized trial in Japan involving 27 patients with active AOSD refractory to glucocorticoids (≥0.5 mg/kg daily of prednisolone or equivalent given for more than two weeks) who were randomly assigned to also receive either tocilizumab (8 mg/kg intravenously every two weeks) or placebo [59]. A higher proportion of patients achieved an American College of Rheumatology (ACR) response criteria for 50 percent improvement in disease activity (ACR50) response at

week 4, although this difference did not reach statistical significance (61.5 percent, 95% CI 31.6-86.1 versus 30.8 percent, 95% CI 9.1-61.4, p = 0.24). At 12 weeks, patients receiving tocilizumab had greater reductions in systemic features of AOSD based upon the systemic features scoring tool used in the study (least square means for change -4.1 versus -2.3, p = 0.003) and greater reductions in glucocorticoid dose (46.2 versus 21.0 percent reduction compared with baseline, p = 0.017).

No serious adverse events were noted in the 12-week blinded portion of the trial; serious adverse effects seen with tocilizumab during the 40-week open-label extension included infections, aseptic necrosis in the hips, exacerbation of the AOSD, drug eruption, and anaphylactic shock, but there were no deaths or episodes of MAS. Limitations of the trial included its small size and some imbalances in baseline characteristics of treatment and control groups.

- The benefits of IL-6 inhibition were described in a multicenter, open-label, retrospective study of 34 patients with AOSD treated with tocilizumab (usually 8 mg/kg administered intravenously every four weeks [22 of 34 patients] or every two weeks [10 of 34 patients]); all patients had failed treatment with glucocorticoids and at least one traditional DMARD (typically MTX), and 50 percent had also received a biologic DMARD, typically a TNF inhibitor or anakinra [61]. Acute phase reactants and systemic manifestations typically improved in the first month of tocilizumab therapy, while the frequency of joint manifestations (arthralgia and/or arthritis) decreased modestly during that interval (from 97 to 68 percent). After one year, the frequency of joint manifestations was reduced to 32 percent. Other findings improved to a greater degree and responses were sustained at one year. Decreases were seen in the frequency of cutaneous manifestations and fever (both from 59 to 6 percent), in lymphadenopathy (from 29 percent to none), and in acute phase reactants. The median dose of prednisone was reduced from 14 to 2.5 mg daily.

  Treatment was permanently discontinued in two patients, both with severe infections (one with pyelonephritis and acute enterocolitis and the other with spondylodiscitis and a psoas abscess due to *Staphylococcus aureus*). Additional, more common adverse effects, none of which required permanent discontinuation of the drug, included other infections (eight cases, including one patient with herpes zoster), mild leukopenia or neutropenia (four patients), and elevated liver enzymes (four patients).

The correlation of elevated IL-6 with arthritic presentation in both sJIA and AOSD has raised the possibility that tocilizumab may be superior to IL-1 blockade in patients with primarily arthritic manifestations [56,64]. Some evidence supports this possibility. A retrospective series of 27 patients found that systemic symptoms in the absence of arthritis predicted good response to IL-1 blockade while an arthritis-dominant phenotype was associated with response to IL-6 blockade [65]. However, no comparable results were identified in a 140-patient series of patients with AOSD treated with IL-1 blockade, and separate trials report similar levels of efficacy of canakinumab and tocilizumab against arthritis

in sJIA, although these agents have not been directly compared [50,55,66].

Due to an enhanced risk of gastrointestinal perforation reported with tocilizumab, we avoid IL-6 blockade in patients with known diverticulosis [67].

Tumor necrosis factor inhibitors — In patients for whom a TNF inhibitor is appropriate, we typically begin with infliximab because the infused route enables maximal dosing, since in our experience patients with AOSD often require high-dose therapy (eg, infliximab 10 mg/kg monthly).

Benefit for patients with AOSD has been reported with etanercept [45,68,69], infliximab [45,69-73], and adalimumab [13,45,74], usually in patients who have experienced an inadequate response to glucocorticoids and MTX. These benefits predominantly affect arthritic features; fever and rash respond inconsistently, and TNF inhibition is not effective for MAS.

The following data illustrate the range of findings:

- Among 12 patients with AOSD resistant to prior DMARD therapy, 7 achieved ACR20 improvement after six months of treatment with etanercept [68]. In three patients with fever and rash at disease entry, only one demonstrated improvement in these disease manifestations.
- Six patients treated with infliximab experienced resolution of their fever, rash, hepatosplenomegaly, arthralgia, and myalgia after the first series of infusions [72]. Glucocorticoid doses were reduced during the follow-up period of 5 to 28 months suggesting that infliximab had been effective. Similar benefits with infliximab were noted in a second study [73].

Case reports and small series indicate that treatment failure, partial response, and loss of efficacy over time are not uncommon [69,75]. This was illustrated in a series of 20 patients with disease refractory to MTX who were treated with etanercept (10 patients), infliximab (15 patients), or both agents sequentially (5 patients) [69]. The following results were noted:

- Complete remissions were observed in 5 patients (1 with etanercept, 4 with infliximab).
- Partial responses were observed in 11 patients (6 with etanercept, 5 with infliximab).
- Despite these initial benefits, 17 patients (85 percent) ultimately discontinued treatment with the TNF inhibitor, most often for loss of efficacy (11 patients).

The potential adverse effects of TNF inhibitors in AOSD, which are described in detail separately, are the same as those in patients with RA. (See "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects".)

REFRACTORY TO STANDARD THERAPIES — For patients with adult-onset Still's disease (AOSD) who fail to respond to well-established therapies, several alternate options can be considered:

- **Janus kinase inhibitors** — We employ Janus kinase (JAK) inhibitors in patients with AOSD for whom conventional nonbiologic and biologic

treatments have proven insufficient to enable symptom control with no more glucocorticoids than prednisone 5 mg daily or equivalent. The JAK proteins mediate intracellular signaling downstream of multiple cytokines and growth factors, including interleukin (IL) 6 and interferons. Limited data suggest that agents in the class may be useful for patients with systemic juvenile idiopathic arthritis (sJIA)/AOSD [76-78].

In the largest series published, 14 patients with AOSD refractory to prednisone and at least one disease-modifying antirheumatic drug (DMARD) were treated with tofacitinib 5 mg twice daily, resulting in remission in seven and partial response in six, as well as a marked reduction of glucocorticoid requirement [79]. Since interferon gamma appears to play a key pathogenic role in macrophage activation syndrome (MAS), JAK inhibitors may be particularly appealing for AOSD patients with a history of MAS. The use, dosing, and adverse effects of JAK inhibitors are described in further detail separately. (See "Treatment of rheumatoid arthritis in adults resistant to initial conventional synthetic (nonbiologic) DMARD therapy", section on 'JAK inhibitor therapy' and "Treatment of rheumatoid arthritis in adults resistant to initial biologic DMARD therapy", section on 'JAK inhibitors' and "Treatment and prognosis of hemophagocytic lymphohistiocytosis" and "Overview of the Janus kinase inhibitors for rheumatologic and other inflammatory disorders".)

- **Other agents**
  - Cyclosporine – Some evidence suggests that cyclosporine is effective in AOSD [7,13,80-83]. We prefer other agents because of the risks associated with cyclosporine use, including nephrotoxicity. The calcineurin inhibitors cyclosporine and tacrolimus are options for treatment of MAS. (See "Pharmacology of calcineurin inhibitors" and "Cyclosporine and tacrolimus nephrotoxicity" and "Treatment and prognosis of hemophagocytic lymphohistiocytosis".)
  - Thalidomide – Thalidomide is effective in some patients with sJIA [84,85]. One report identified efficacy in a case of AOSD [86]. Teratogenicity, neuropathy, and cost represent barriers to use, but thalidomide could be considered in carefully selected patients with refractory AOSD.
  - Rituximab – Limited data suggest that rituximab, a chimeric monoclonal antibody that depletes peripheral B cells for 6 to 12 months or longer, may be of benefit for the treatment of AOSD that is refractory to other biologic agents [87]. It was reported as effective in AOSD complicated by thrombotic microangiopathy [88]. It is widely used for the treatment of rheumatoid arthritis (RA). (See "Rituximab: Principles of use and adverse effects in rheumatoid arthritis".)
  - Intravenous immune globulin – Intravenous immune globulin has been administered to patients with AOSD, with sustained benefit reported in some patients, particularly in the context of MAS [89-93]. (See "Overview of intravenous immune globulin (IVIG) therapy".)

- Tadekinig alfa – A recombinant IL-18 binding protein, tadekinig alfa is an investigational agent that has shown preliminary evidence of efficacy in some patients with AOSD [94]. This agent is not yet commercially available.
- Cyclophosphamide - Cyclophosphamide has been employed successfully in AOSD at the case-report level, including in patients with MAS [93,95].
- Combination biologic therapy – This approach is typically avoided because of concerns over synergistic immunosuppression; combination biologics have been employed for some patients with refractory sJIA/AOSD, including anakinra with abatacept and anakinra with the JAK inhibitor baricitinib [77,96].
- Allogeneic bone marrow transplantation – Bone marrow transplantation (allogeneic) has been reported as effective in some patients with refractory sJIA [97,98]. Autologous transplantation has also been reported [97,99,100]. Treatment-related morbidity and mortality remain an important concern for this approach.

MONITORING

Disease and drug monitoring — Monitoring of the response to therapy includes assessment at regular intervals of the clinical and laboratory response as well as for adverse effects of medications. Patients with new-onset and exacerbations ("flares") of adult-onset Still's disease (AOSD) generally need to be seen at least every two to four weeks depending upon treatment and clinical status.

Patients on a stable medical regimen who are doing well clinically are generally seen every three to four months. Clinical, laboratory, and radiologic monitoring of disease activity and joint injury is otherwise similar to that performed in patients with rheumatoid arthritis (RA). (See "General principles and overview of management of rheumatoid arthritis in adults", section on 'Assessment and monitoring' and "General principles and overview of management of rheumatoid arthritis in adults", section on 'Clinical assessment of disease and related testing'.)

Particular attention is given to the following:

- **Medical history** – Patients should be asked about fever, rash, new joint swelling, sore throat, and other symptoms that had characterized the patient's illness when disease was active.
- **Laboratory testing** – We obtain blood for a complete blood count (CBC), blood urea nitrogen and creatinine, electrolytes, ferritin, D-dimer, and alanine and aspartate aminotransferases (ALT, AST; and additional liver function studies if abnormalities are seen).

  Given reports of hepatotoxicity attributed to anakinra, we monitor liver enzymes within two weeks after starting this medication and every two to four months thereafter [101,102].

Additional monitoring with most of these studies for macrophage activation syndrome (MAS) is also indicated in patients starting a new medication. (See 'Monitoring for MAS' below.)

- **Monitoring for complications of AOSD** – Certain conditions may occur as complications during the course of treatment of AOSD. These include MAS and possibly an AOSD-associated lung disease similar to a condition found in some patients with systemic juvenile idiopathic arthritis (sJIA). We closely monitor for MAS during the early stages of treatment with the introduction of any agent and continue to have a low threshold for considering MAS in any patient with AOSD. (See 'Monitoring for MAS' below and 'Monitoring for lung disease' below.)

Information regarding the adverse effects of medications in AOSD is derived from case reports, small case series, and a very small number of randomized trials, as well as extrapolation from sJIA.

Monitoring for MAS — Regular monitoring for MAS is prudent when initiating any new treatment for AOSD with active systemic features since MAS is a leading cause of death in patients with AOSD [103]. MAS can occur at any time, even when a patient's disease is well controlled on biologic therapies, and can occur without an obvious trigger [104]. There are no data, other than the infrequent reports of MAS associated with certain drug therapies, to indicate any special or novel concerns regarding the agents used in the treatment of AOSD. However, in patients receiving interleukin (IL) 1 or IL-6 blockade, MAS may initially present with attenuated clinical and laboratory features [105].

A high degree of suspicion should be maintained as clinical features of MAS may strongly resemble features of AOSD. The appearance of MAS in patients with AOSD is typically heralded by a recurrence of systemic symptoms, including fever and rash, although this is not invariably the case. The physical examination may reveal lymphadenopathy and/or hepatosplenomegaly.

In patients starting a new medication for AOSD, including nonsteroidal antiinflammatory drugs (NSAIDs), we obtain the following laboratory studies every two weeks initially and with any escalation of the dose:

- CBC, differential white count, and platelet count
- AST and ALT
- Ferritin
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- D-dimer

The most specific routine laboratory finding is ferritin, which frequently rises to levels >5000 ng/L, although concomitant therapy with tocilizumab and, to a lesser extent, IL-1 blockers can blunt this rise [105]. CRP rises as a reflection of inflammation, though the ESR may fall paradoxically through fibrinogen consumption, leading to a marked increase in the ratio between ferritin and ESR [106]. D-dimer reflects intravascular coagulation; commonly elevated in active sJIA/AOSD, a marked increase is typically seen in MAS. Additional changes in routine laboratory studies include leukopenia, anemia, thrombocytopenia, and

increases in hepatic transaminases [10].

The frequency of testing can be decreased to monthly if the dose is stable and if the aminotransferases remain within the normal range. Testing can be decreased to every three months after the liver function studies have remained normal for at least three months on a stable drug regimen.

Patients suspected of MAS should be immediately referred for consultation with a rheumatologist or hematologist with expertise in hemophagocytic syndromes associated with autoimmune and inflammatory diseases. (See "Clinical manifestations and diagnosis of adult-onset Still's disease", section on 'Macrophage activation syndrome' and "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis", section on 'Triggers' and "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis", section on 'Rheumatologic disorders/MAS'.)

Monitoring for lung disease — Clinicians should be attentive to a novel and potentially serious pulmonary complication of sJIA, and possible AOSD, described since the early 2000s in case reports and case series; in sJIA, this has been termed sJIA-lung disease (sJIA-LD) [107-109]. Lung disease in patients with AOSD was reported in one series in 18 of 147 patients, in whom it was associated with higher mortality, typically from refractory MAS rather than the lung disease itself; whether these cases correspond to sJIA-LD is unclear [110]. However, clinicians caring for patients with AOSD, especially those receiving IL-1 or IL-6 inhibitors, should be aware of this association, although risk in patients with AOSD is not fully defined [111].

In sJIA this syndrome has been found most commonly in patients whose disease begins at a young age (many under two years) and who have a history of episodes of MAS; laboratory correlates include elevation of IL-18 and, in many patients, a striking eosinophilia [108,109]. Further clinical associations include trisomy 21, erythematous clubbing of the digits, and, in 30 percent, a history of anaphylactic-type reactions to infused tocilizumab [109]. Most but not all affected children have received IL-1 inhibitors and often also IL-6 inhibitors, raising the possibility that sJIA-LD could represent a complication of therapy or, alternately, of reduced use of glucocorticoids and methotrexate (MTX) [109,111].

MEDICATION TAPERING AND DURATION OF THERAPY — A substantial portion of patients with adult-onset Still's disease (AOSD) are ultimately able to come entirely off therapy, unlike patients with other chronic inflammatory rheumatic diseases such as rheumatoid arthritis (RA) (see "Clinical manifestations and diagnosis of adult-onset Still's disease"). Some of these patients may have been destined to experience a "monocyclic" form of AOSD (analogous to monocyclic systemic juvenile idiopathic arthritis [sJIA]). It is possible that aggressive therapy given during a "window of opportunity" in early disease may favorably impact the disease course [12,16,20]. Protocols for tapering and discontinuation of disease-modifying antirheumatic drugs (DMARDs) in AOSD are not available.

For patients in complete remission for at least three months, we gradually taper medications with the goal of drug discontinuation. Conventional synthetic

DMARDs such as methotrexate (MTX) are typically weaned by a gradual reduction of the dose by 2.5 to 5 mg every two to three months, whereas for biologic agents, extending the interval between doses may be modestly preferable [16,112,113].

As examples, we take the following approach to tapering of biologic DMARDs based upon our clinical experience and that of other experts:

- Anakinra – We wean anakinra to every other day for one month followed by discontinuation, cautioning patients to keep 7 to 14 doses of anakinra on hand to allow immediate resumption of treatment if disease recurs [16].
- Canakinumab – For canakinumab, we increase the interval from monthly to every other month for two infusions and then to every three months for two infusions before discontinuing [112].
- Tocilizumab – For tocilizumab, we space injections from weekly to every other week for two months and then to monthly for two months before discontinuing; infusions are spaced to monthly and then every other month (two infusions at each step) before ending therapy.

In patients in whom disease recurs, we return to full-intensity therapy to regain control before tapering again to the lowest tolerated dose or dose frequency.

TREATMENT OF RELAPSE — The treatment of choice in a patient who relapses while on therapy or after discontinuation of treatment depends upon the symptoms and findings, including the extent and severity of organ system involvement, as well as the intensity of the inflammatory response:

- **Flare during tapering** – Increasing medication doses to the level previously effective may be adequate in patients who flare during the tapering of medications. (See 'Medication tapering and duration of therapy' above and 'Subsequent therapy: Established disease' above.)
- **Mild symptoms** – In general, mild symptoms can be addressed using nonsteroidal antiinflammatory drug (NSAIDs). (See 'Mild to moderate disease' above and 'Treatment approach' above.)
- **Systemic symptoms** – Systemic symptoms such as fever and rash require biologic therapy and/or glucocorticoids, with careful monitoring for incipient macrophage activation syndrome (MAS). (See 'Monitoring for MAS' above.)
- **Arthritis** – Arthritis can be addressed by conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) or leflunomide (LEF), or by institution or change in biologic therapy (favoring interleukin [IL] 6 blockade). Incipient or active MAS requires glucocorticoids, often together with IL-1 blockade or other agents. In patients who flare during the tapering of medications, increasing medication doses to the level previously effective may be adequate. (See 'Initial therapy: New-onset disease' above and 'Subsequent therapy: Established disease' above.)
- **Severe disease** – In patients with severe relapses or with the new development of life-threatening disease manifestations, a modification of

therapy to incorporate an approach similar to that used for initial severe disease may be required, depending upon the specific medications to which the patient has previously responded or with which they are being treated at the time of the clinical change. (See 'Initial therapy: New-onset disease' above and 'Subsequent therapy: Established disease' above.)

PROGNOSIS — The functional status of patients with adult-onset Still's disease (AOSD) is often good, even in the setting of a chronic disease pattern. Several predictors of chronic disease and of an unfavorable outcome have been described in AOSD [14,114,115]:

- Development of an erosive polyarthritis during the initial presenting episode of disease
- Involvement of the shoulders or hips
- A history of macrophage activation syndrome (MAS)
- A history of cardiac involvement, including pericarditis

Prior to routine use of biologics, the need for more than two years of systemic glucocorticoid therapy was also a poor prognostic factor.

In one series published in 1991 of 62 patients with AOSD, 36 percent had a chronic disease course, but 90 percent were judged to be American College of Rheumatology (ACR) Functional Class 1 (able to perform usual activities of daily living, including self-care, vocational, and avocational activities) [14,116]. In findings published in 1987, polyarticular onset and chronic joint involvement were associated with a poorer functional outcome, but systemic symptoms were not; joint arthroplasty significantly improved the functional status of AOSD patients with chronic destructive arthritis [15]. These observations were made prior the standard use of biologic agents in this condition. No prospective long-term studies of patients with AOSD receiving early biologic therapy are available.

Chronic active inflammation resistant to treatment can lead to AA (secondary) amyloidosis [117-119]. Use of anti-interleukin (IL) 1 therapies may prevent progression of amyloid but may not treat extant disease [120]. (See "Causes and diagnosis of AA amyloidosis and relation to rheumatic diseases".)

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Adult-onset Still's disease".)

SUMMARY AND RECOMMENDATIONS

- **New-onset adult-onset Still’s disease (AOSD)**
  - **Mild disease** – For patients with mild disease, such as fevers, rash, arthralgias, or mild arthritis, and in the absence of macrophage activation syndrome (MAS), we suggest initial therapy with antiinflammatory doses of a nonsteroidal antiinflammatory drug (NSAID) rather than glucocorticoids or conventional or biologic disease-modifying antirheumatic drugs (DMARDs) (**Grade 2C**). An antiinflammatory dose and regimen should be used (eg, naproxen [500 mg twice daily], ibuprofen [800 mg three times daily]). (See 'Approach to initial therapy'

above and 'Mild to moderate disease' above.)

- **Moderate to severe disease** – For patients with moderate to severe AOSD, which may include serositis, debilitating arthritis, fevers refractory to NSAIDs, or internal organ involvement, and for patients in whom two weeks of NSAIDs are insufficient, we suggest anakinra rather than either NSAIDs alone, glucocorticoids, or another DMARD (**Grade 2C**). Our usual initial dose is 100 mg subcutaneously daily. Glucocorticoids (20 to 60 mg orally daily, depending upon the severity of disease and the initial response) are a reasonable alternative if anakinra is unavailable. (See 'Approach to initial therapy' above and 'Moderate to severe disease' above.)

- **Concern for MAS** – For patients in whom incipient or active MAS remains a concern, we suggest combining anakinra with glucocorticoid therapy, rather than using a single agent (**Grade 2C**). (See 'Concern for incipient or active MAS' above.)

- **Management of established disease**

  - **Glucocorticoid-sparing therapy** – For patients unable to reduce glucocorticoids to ≤10 mg daily of prednisone (or equivalent) after one month of therapy, we suggest the addition of a glucocorticoid-sparing DMARD rather than continuing the same level of glucocorticoid therapy (**Grade 2C**). (See 'Treatment approach' above and 'Glucocorticoid-sparing therapy for chronic management' above.).

    - For patients with arthritis (including any evidence of erosive joint disease on joint radiographs), we prefer methotrexate (MTX). Alternatives to MTX include leflunomide (LEF) and tocilizumab or other interleukin (IL) 6 inhibitor. (See 'Methotrexate and other conventional DMARDs' above and 'Interleukin 6 inhibition' above.)

    - For patients with arthritis that has not responded to conventional DMARDs (MTX or LEF) and who are also refractory to IL-1 and IL-6 inhibition, a tumor necrosis factor (TNF) inhibitor may be used; we limit its use in AOSD to refractory arthritis. (See 'Tumor necrosis factor inhibitors' above.)

    - For patients with predominantly systemic symptoms and/or suspected incipient MAS, we prefer anakinra, an IL-1 inhibitor. Canakinumab is a reasonable alternative to anakinra. (See 'Anakinra' above.)

  - **Monitoring** – Monitoring of the response to therapy includes assessment at regular intervals of the clinical and laboratory response as well as for adverse effects of medications. Usual laboratory monitoring includes a complete blood count (CBC), blood urea nitrogen and creatinine, electrolytes, ferritin, D-dimer, and alanine and aspartate aminotransferases (ALT, AST). (See 'Disease and drug monitoring' above and 'Monitoring for MAS' above.)

- **Duration of therapy** – For patients in complete remission for at least three months, we gradually taper medications with the goal of drug discontinuation. (See 'Medication tapering and duration of therapy' above.)
- **Treatment of relapse** – Treatment for patients who relapse while on therapy or after discontinuation of treatment depends upon the symptoms and findings, including the extent and severity of organ system involvement, as well as the intensity of the inflammatory response. Increasing medication doses to the level previously effective may be adequate in patients who flare during the tapering of medications. (See 'Treatment of relapse' above.)

ACKNOWLEDGMENT — The UpToDate editorial staff acknowledges John M Esdaile, MD, who contributed to an earlier version of this topic review.

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