Anakinra for the treatment of adult secondary HLH: a retrospective experience

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Abstract
Anti-cytokine therapies have been gaining attention as a means of improving outcomes in adult secondary HLH (asHLH), which currently has poor outcomes when treated with standard etoposide-based therapies. Anakinra is an interleukin-1 antagonist that is increasingly being used in the management of asHLH. Here is described a multi-hospital series of 16 adult patients with secondary HLH treated with anakinra. Provoking factors of secondary HLH included hematologic malignancy (n = 7, 44%), bacterial infection (n = 7, 44%), viral infection (n = 5, 31%), rheumatologic disorder (n = 4, 25%), and unknown (n = 1, 6%). Five patients remained alive at time of last follow-up (OS = 31%). Median OS was 1.7 months from initiation of anakinra (range 0.2–59). OS among patients with rheumatologic causes of secondary HLH was 75%, whereas only 17% of patients with other provoking factors survived (p = 0.0293). Anakinra was well tolerated, with only 1 patient experiencing associated toxicity (grade 3 liver injury). Anakinra may be useful in the management of asHLH provoked by rheumatologic conditions, although its benefit in asHLH provoked by other factors may be limited.

Keywords HLH · Adult HLH · Secondary HLH · Anti-cytokine therapy · Anakinra

Introduction
Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of excessive and maladaptive inflammation [1]. HLH may arise in the setting of a demonstrable immune-dysregulating gene mutation, and in such instances is referred to as “primary HLH”. The syndrome may also occur in the absence of any identifiable genetic lesion, and arise as a disproportionate inflammatory response to a provoking immunogenic stimulus [2]. Such cases are referred to as “secondary HLH”. Primary HLH occurs almost exclusively among infants and young children, and has been shown to respond favorably to a treatment regimen which employs etoposide, corticosteroids, and subsequent allogeneic bone marrow transplant (a protocol known as HLH-94) [3]. Secondary HLH occurs more commonly among adults, and in spite of efforts to adapt the pediatric HLH-94 protocol to such patients, outcomes remain dismal [4]. Overall survival (OS) rates in adult secondary HLH are typically reported to be in the range of 25–40%, and the use of etoposide-based therapy has not been shown to significantly improve outcomes when compared to treating the underlying trigger (such as malignancy, infection, or rheumatologic disease) alone [4–7]. Given the lack of success with etoposide-based therapy in adult secondary HLH, interest has grown in the use of anti-inflammatory or cytokine-directed therapies [8]. Indeed, HLH physiology has often been described as a state of “cytokine storm”, and profound and dysregulated cytokinemia is a hallmark of the condition [8]. At many centers, anti-inflammatory cytokine-directed therapies are now given as early-line interventions in cases of suspected adult secondary HLH. Often, such therapies are used off-label in an attempt to salvage severely ill and deteriorating patients who fail to respond appropriately to treatment of their triggering pro-inflammatory condition alone. Among the most often used anti-cytokine agents in the management of HLH is the interleukin-1 (IL-1) antagonist anakinra [9]. However, data regarding the efficacy and safety of anakinra in adult secondary HLH remains scarce, and its utility in this condition remains poorly defined. Herein is described an institutional experience of the use of anakinra in the treatment of adult secondary HLH.
Materials and methods

This retrospective study was approved by the internal review board (IRB) of the Mount Sinai Hospital. The need for patient consent was waived given the retrospective nature of the study and that all patient data was de-identified. The medical records of an urban multihospital system (the Mount Sinai Health System in New York City) were searched to identify all adult patients (age >18 years), seen during inpatient admissions between January 1, 2009, and January 1, 2022, who received anakinra for a diagnosis of secondary HLH. Each medical record was reviewed to confirm a diagnosis of secondary HLH (via fulfillment of at least 5/8 HLH-2004 criteria in the absence of any family history or identified genetic lesion indicative of primary HLH). Patients were excluded if they met <5/8 HLH-2004 criteria, if they had evidence of primary HLH (a demonstrated mutation in a known HLH-causative gene or known family history of HLH), if they did not receive anakinra for the treatment of HLH, or if documentation regarding their characteristics, treatment, and/or outcomes was incomplete. Patients were followed from time of diagnosis of HLH, until time of death or time of last follow-up. Data were collected regarding patient demographics, potential HLH triggers, baseline characteristics, treatment characteristics, and outcomes. The primary outcome of interest was survival. The secondary outcome was maximum ferritin response (determined by dividing maximum ferritin decrease after starting anakinra by ferritin level on day 1 of anakinra). Continuous patient-related, disease-related, and treatment-related variables were summarized by the median and range, while categorical variables were summarized by N (%). Distributions of continuous and categorical variables were compared using the Mann–Whitney U test and χ² test, respectively.

Results

One-hundred-nineteen adult inpatients with secondary HLH, diagnosed on the basis of meeting at least 5/8 HLH-2004 criteria, were identified during the study period. Of these patients, 16 received anakinra, and were therefore included in this study. The baseline characteristics, treatment characteristics, and outcomes among these 16 included patients are shown in Table 1. Seven patients (44%) were female. The median age was of 40.5 years (range 19–82). Confirmed or presumed provoking factors of secondary HLH included hematologic malignancy (n = 7, 44%), bacterial infection (n = 7, 44%), viral infection (n = 5, 31%), rheumatologic disorder (n = 4, 25%), and unknown (n = 1, 6%). Six patients (38%) had more than one apparent provoking factor for secondary HLH. All patients met at least 5 HLH-2004 criteria (median number of criteria met = 5, range 5–7). The median H-score was 208 (range 178–238) [10]. The median ferritin on the day of anakinra initiation was 38,052 ng/ml (range 1458–144,361 ng/ml).

The median hospital-day of HLH diagnosis was 11.5 (range 1–38). Thirteen patients (81%) received some form of HLH-directed therapy prior to starting anakinra. Prior therapies included corticosteroids (n = 12, 75%), etoposide (n = 3, 19%), tocilizumab (n = 2, 13%), ruxolitinib (n = 1, 5%), and IVIG (n = 1, 6%). The median hospital-day on which anakinra was initiated was 12.5 (range 6–39). All patients received anakinra subcutaneously. Patients received anakinra at dosage schedules ranging from once daily to once every 6 h. The median total daily dosage of anakinra was 350 mg (range 100–600 mg). The median number of days on anakinra was 12 (range 5–61). Twelve patients (75%) received some form of concurrent HLH-directed therapy along with anakinra. Concurrent therapies included corticosteroids (n = 12, 75%), etoposide (n = 2, 13%), and ruxolitinib (n = 1, 6%). Thirteen patients (81%) received concurrent treatment for their underlying cause(s) of HLH while receiving anakinra.

Median follow-up was 1.65 months (range 0.2–59 months). Five patients remained alive at time of last follow-up (overall survival (OS) = 31%). Median OS was 1.7 months from initiation of anakinra (range 0.2–59). Survivors were relatively young although the age difference between survivors and non-survivors was not significant (median age among survivors was 32 years vs 61 years among non-survivors, p = 0.174). Survival by provoking cause of secondary HLH included; hematologic malignancy 1/7 (14%), bacterial infection 0/7 (0%), viral infection 0/5 (0%), rheumatologic disorder 3/4 (75%), and unknown 1/1 (100%). The distribution of provoking causes of secondary HLH (hematologic malignant, viral infection, bacterial infection, rheumatologic, other) differed significantly between survivors and non-survivors on χ² analysis (p = 0.00652), with survivors having a notably greater proportion of rheumatologic cases. OS among patient with a rheumatologic cause of secondary HLH was 75%, whereas only 17% of patients with other causes of secondary HLH survived (p = 0.00293). No other baseline or treatment characteristics were significantly different between survivors and non-survivors.

Patient ferritin levels at time of initiation of anakinra (day 1), subsequent ferritin levels during/following treatment with anakinra, and max ferritin response (determined by dividing maximum ferritin decrease after starting anakinra by ferritin level on day 1 of anakinra), are shown in Table 2. There was no significant difference in baseline (day 1) ferritin levels between survivors and non-survivors. Survivors did however
Table 1 The baseline characteristics, treatment characteristics, and outcomes of all included patients are summarized

| Patient | Age | Sex | Cause of secondary HLH | HLH 2004 Criteria Met | H Score | Ferritin (ng/ml) | Prior HLH-directed therapy | Concurrent HLH-directed therapy | Concurrent treatment of cause of HLH | Hospital day of HLH diagnosis | Hospital day anakinra started | Anakinra dose/route | Days on anakinra | Anakinra toxicity | Survival Months |
|---------|-----|-----|------------------------|-----------------------|--------|----------------|---------------------------|-------------------------------|---------------------------------|-------------------------------|-----------------------------|------------------|-----------------|-----------------|-----------------|----------------|
| 1       | 65  | F   | myelofibrosis in blast phase, enterococcus bacteremia | 5                     | 206    | 109,988        | Dexa-methasone 40 mg daily, ruxolitinib 10 mg bid | Dexa-methasone 40 mg daily, ruxolitinib 10 mg bid | Antibiotics, decitabine       | 1                             | 10                           | 100 mg subq q8 | 8               | None            | No              | 0.3             |
| 2       | 70  | M   | multiple myeloma, enterococcus bacteremia, CMV viemia | 5                     | 202    | 4338           | Methylprednisolone 60 mg daily, tocilizumab           | None                           | Antibiotics, antivirals        | 25                            | 38                           | 100 mg subq q12 | 9               | None            | No              | 1.5             |
| 3       | 25  | M   | hepatosplenic T-cell lymphoma | 7                     | 238    | 131,063        | Dexa-methasone 20 mg daily, etoposide (part of ICE protocol) | Dexa-methasone 20 mg daily | ICE chemotherapy protocol     | 21                            | 22                           | 100 mg subq q8 | 18              | None            | No              | 1.8             |
| 4       | 32  | F   | anaplastic large cell lymphoma | 6                     | 210    | 11,897         | None                                                   | Dexa-methasone 20 mg daily, etoposide (part of CHOEP protocol) | CHOEP chemotherapy protocol | 9                             | 9                            | 100 mg subq q8 | 12              | None            | Yes             | 57              |
Table 1 (continued)

| Patient | Age | Sex | Cause of secondary HLH | HLH 2004 Criteria Met | H Score | Ferritin (ng/ml) | Prior HLH-directed therapy | Concurrent HLH-directed therapy | Concurrent treatment of cause of HLH | Hospital day of HLH diagnosis | Hospital day anakinra started | Anakinra dose/route | Days on anakinra | Anakinra toxicity | Survival Months survival |
|---------|-----|-----|--------------------------|-----------------------|---------|------------------|-----------------------------|-------------------------------|----------------------------------|-------------------------------|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| 5       | 27  | M   | chronic EBV associated NK/T-cell lymphoma | Met                  | 229    | 79,812           | Dexamethasone 40 mg daily, etoposide | Dexamethasone 20 mg daily, etoposide | Modified SMILE chemotherapy protocol, rituximab | 3                              | 11                          | 200 mg subq q12 | 5               | None            | No              | 0.2             |
| 6       | 82  | M   | CLL in Richter's transformation, enterovirus infection | 5                    | 196    | 39,812           | Dexamethasone 10 mg daily | None | None | 7                              | 10                          | 200 mg subq q8       | 5               | None            | No              | 0.2             |
| 7       | 39  | M   | Hodgkin's lymphoma, EBV viremia, cholangitis | 6                    | 212    | 133,511          | Dexamethasone 40 mg daily, etoposide | Dexamethasone 20 mg daily | Antibiotics, rituximab | 1                              | 8                           | 100 mg subq q6      | 8               | None            | No              | 0.3             |
| Primary infectious etiology | 8 | 62 | F | septic shock (presumed, organism unknown) | 6 | 220 | 10,287 | None | None | Antibiotics | 23 | 24 | 100 mg subq q8 | 7 | None | No | 0.3 |
| 9       | 42  | M   | septic shock (presumed, organism unknown) | 5                    | 184    | 144,361          | Tocilizumab | Dexamethasone 20 mg daily | Antibiotics | 38 | 39 | 200 mg subq daily | 20 | None | No | 1.8 |
| 10      | 61  | F   | Multi-organism sepsis | 5                    | 189    | 4054            | None | Dexamethasone 10 mg daily | Antibiotics | 19 | 21 | 200 mg subq q8 | 61 | None | No | 2.1 |
**Table 1 (continued)**

| Patient | Age | Sex | Cause of secondary HLH | HLH 2004 Criteria Met | H Score | Ferritin (ng/ml) | Prior HLH-directed therapy | Concurrent HLH-directed therapy | Concurrent treatment of cause of HLH | Hospital day of HLH diagnosis | Hospital day anakinra started | Anakinra dose/route | Days on anakinra | Anakinra toxicity | Survival Months |
|---------|-----|-----|-------------------------|-----------------------|---------|-----------------|---------------------------|-------------------------------|--------------------------------|------------------------------|-------------------------------|---------------------|------------------|-----------------|----------------|
| 11      | 64  | M   | COVID19 pneumonia, pseudomonal sepsis | Met                   | 6       | 199             | Dexamethasone 20 mg daily | Dexamethasone 20 mg daily | Antibiotics                    | 26                           | 29                            | 200 mg subq q8      | 12               | None            | No              | 0.5            |
| 12      | 34  | M   | suspected rheumatologic disorder (diagnosis unclear) | 5                     | 181     | 28,911          | Prednisone 80 mg daily | Prednisone 80 mg daily | Prednisone 80 mg daily       | 9                            | 10                            | 200 mg subq q8      | 14               | None            | Yes             | 29            |
| 13      | 32  | F   | systemic lupus erythematosus, autoimmune hepatitis | 5                     | 218     | 65,981          | Methylprednisolone 100 mg daily | Methylprednisolone 100 mg daily | Hydroxychloroquine           | 5                            | 6                             | 200 mg subq q8      | 13               | None            | Yes             | 59            |
| 14      | 19  | F   | suspected rheumatologic disorder (diagnosis unclear) | 5                     | 178     | 1458            | Prednisone 40 mg daily | None                          | None                          | 14                           | 14                            | 100 mg subq q12     | 32               | None            | No              | 1.3           |
| 15      | 56  | F   | undifferentiated rheumatologic disorder (possible Still's disease) | 5                     | 218     | 88,905          | Prednisone 60 mg daily | Solumedrol 1 g daily | Solumedrol 1 g daily         | 5                            | 6                             | 100 mg subq daily   | 5                | Acute liver injury (grade 3) | Yes             | 4             |
| Other   | 16  | 24  | unknown                 | 7                     | 231     | 9346            | Prednisone 90 mg daily | Dexa-methasone 20 mg daily | None                          | 15                           | 28                            | 200 mg subq q8      | 31               | None            | Yes             | 49            |

*CHOEP* cyclophosphamide–hydroxydaunorubicin–oncovin–etoposide–prednisone, *CLL* chronic lymphocytic leukemia, *CMV* cytomegalovirus, *COVID19* coronavirus disease 2019, *EBV* Epstein–Barr virus, *HLH* hemophagocytic lymphohistiocytosis, *ICE* ifosfamide–carboplatin–etoposide, *SMILE* steroid–methotrexate–ifosfamide–lasparaginase–etoposide, *subq* subcutaneous
Table 2  Ferritin levels at start of anakinra (deemed day 1) and subsequent ferritin levels (on days 1–50 after start of anakinra) are summarized where available

| Patient | Survival | Months survival | Max ferritin response | Ferritin (ng/ml) |
|---------|----------|-----------------|----------------------|-----------------|
|         |          |                 |                      | Day 1 | Day 5 | Day 10 | Day 15 | Day 20 | Day 25 | Day 30 | Day 35 | Day 40 | Day 45 | Day 50 |
| Primary hematologic malignant etiology | 1 | No | 0.3 | 30% | 109,988 | 76,905 |
| 2 | No | 1.5 | None | | 4338 | 5198 |
| 3 | No | 1.8 | 96% | 131,063 | 91,139 | 22,450 | 12,909 | 63,37 | 10,281 | 83,67 | 93,72 | 56,28 | 93,37 | 19,069 |
| 4 | Yes | 57 | 79% | 11,897 | 37,71 | 3,322 | 2,532 | | |
| 5 | No | 0.2 | 20% | 79,812 | 64,007 | |
| 6 | No | 0.2 | None | 39,812 | 53,100 | |
| 7 | No | 0.3 | 71% | 133,511 | 79,803 | 39,206 | |
| Primary infectious etiology | 8 | No | 0.3 | None | 10,287 | 291,504 | |
| 9 | No | 1.8 | 87% | 144,361 | 75,034 | 79,258 | 57,126 | 18,072 | 28,319 | 33,511 | 58,730 | 103,881 |
| 10 | No | 2.1 | 22% | 40,54 | 46,04 | 4,706 | 3,167 | 6,245 | 5,121 | 10,463 | 4,395 | 8,216 | 16,821 | 10,367 |
| 11 | No | 0.5 | 23% | 36,291 | 67,904 | 37,206 | 28,099 | |
| Primary rheumatologic etiology | 12 | Yes | 29 | 99% | 28,911 | 19,006 | 41,043 | 983 | 491 | 368 |
| 13 | Yes | 59 | 99% | 65,981 | 49,106 | 35,401 | 27,153 | 14,305 | 10,475 | 10,389 | 12,720 | 6137 |
| 14 | No | 1.3 | 53% | 14,58 | 13,85 | 10,69 | 797 | 688 | 12,22 | 12,84 | 19,65 | 1132 |
| 15 | Yes | 4 | 88% | 88,905 | 49,508 | 24,428 | 13,883 | 10,475 | 10,389 | 12,720 | |
| Other | 16 | Yes | 49 | 72% | 93,46 | 75,70 | 66,06 | 56,06 | 48,79 | 39,90 | 33,95 | 31,34 | 25,34 | 26,91 | 25,95 |

Max ferritin response was determined by dividing maximum ferritin decrease after starting anakinra by ferritin level on day 1 of anakinra. A max ferritin response of “none” denotes that ferritin did not decrease after starting anakinra.
demonstrate a greater max ferritin response than did non survivors [median max ferritin response survivors 88% (range 72–99%) vs. non survivors 23% (range 0–96%), p = 0.0128]. Of note although patients with rheumatologic etiology of secondary HLH demonstrated similar baseline ferritin levels to those with all other etiologies, a rheumatologic cause of HLH was associated with greater max ferritin response than all other causes [median max ferritin response rheumatologic patients 94% (range 53–99%) vs. non-rheumatologic patients 27% (range 0–96%), p = 0.0332].

Anakinra was well tolerated with only one patient (6%) suffering a drug-related adverse event (grade 3 acute liver injury). Of note, this patient was on a relatively low dose of anakinra (100 mg daily) and liver injury resolved following discontinuation of anakinra.

Discussion

Adult HLH patients have been consistently shown to have striking early mortality with 20–40% dying within 30 days of diagnosis [5, 11, 12]. Median survival times among adult HLH patients have typically been reported to be in the range of 1–4 months, with fewer than a third of patients surviving follow-up in most studies [4–7, 13]. Treatments in these studies have largely been those targeting the underlying trigger of secondary HLH, with or without concurrent etoposide-based therapy. Across these studies, the addition of etoposide-based therapy has not demonstrated clear benefit when compared with treatment of the underlying pro-voking factor alone [4–7, 12]. In this study, the addition of anakinra yielded an OS of 1.7 months, similar to that which has been reported with treatment of the underlying trigger of HLH alone, and to that which has been reported with etoposide-based therapy. These findings cast some doubt onto the utility of anakinra in adult secondary HLH. However, among the subgroup of patients with a rheumatologic trigger of secondary HLH, OS was 75% (significantly higher than that among patients with HLH due to all other etiolo-gies), suggesting the potential utility of anakinra among this specific group of HLH patients.

Given the well described cytokinemia central to the pathophysiology of HLH, it is unsurprising that there has been strong interest in novel cytokine-directed therapies. Anakinra was among the earliest cytokine blockers used in the management of HLH (although much of its use in this context remains off-label). It has shown impressive efficacy in pediatric secondary HLH, particularly in macrophage activation syndrome (MAS, or secondary HLH due to a rheumatologic trigger). In a single-center series of 8 critically ill pediatric patients who received anakinra as first line therapy for secondary HLH, OS was 88% [14]. Of note, the underlying triggers for secondary HLH among these patients was not described. In a single-center series of 44 pediatric patients with secondary HLH, OS was 73%, and earlier initiation of anakinra was associated with improved survival [15]. A large proportion of this cohort (64%) had an underlying autoimmune or rheumatologic trigger for secondary HLH and an additional 23% had no evident trigger. Those patients with an underlying rheumatologic trigger had the lowest mortality rate, while patients with other triggers had significantly higher mortality rates (and those with underlying hematologic malignancy had a 100% mortality rate). In a single-center series of 19 pediatric patients with MAS treated with intravenous anakinra, OS was 74% [16]. In a two-center series of 12 patients with MAS treated with anakinra, OS was 100% [17]. Anakinra was well-tolerated and demonstrated minimal toxicity across all above studies.

It must be emphasized however that pediatric and adult HLH are fundamentally different diseases, and pediatric HLH data cannot be easily extrapolated to the treatment of adult HLH patients. In children, HLH is often caused by congenital immune abnormalities or EBV-related viruses, while adults adults HLH secondary to hematologic malignancies and/or bacterial sepsis is far more common. Therefore, encouraging findings among pediatric cohorts are not sufficient to justify anakinra’s use among adult patients. The adult literature regarding use of anakinra in secondary HLH is somewhat more limited than the pediatric, with described cohorts typically smaller. Reported survival rates have appeared better than those previously reported with etoposide-based therapy, with the benefit of anakinra most-apparent in those cohorts enriched in rheumatologic cases (MAS). Previously described cohorts of adult secondary HLH patients treated with anakinra are summarized in Table 3. In a cohort of 13 adults with secondary HLH treated with anakinra, OS was 69% [18]. The majority of this cohort (62%) had an autoimmune or rheumatologic trigger and OS was particularly high in this subgroup (88%), compared with 40% among the 5-patients with non-MAS HLH [18]. Similarly, in a cohort of five patients, four of which had an autoimmune or rheumatologic cause of HLH, OS was 80% (notably anakinra was given via continuous intravenous infusion) [19]. Outcomes have been less impressive in those cohorts with relatively fewer MAS patients, and relatively greater proportions of patients with malignant and/or infectious triggers [20, 21]. Although one series did report an OS of 63% among adult patients with HLH secondary to COVID-19 infection (notably anakinra was give via the intravenous route) [22]. As in the pediatric series, in the adult series anakinra was well tolerated with minimal evident toxicity or immunosuppression.

The OS reported in this series (31%) is lower than that reported in those above. This is likely because this series contained a relatively small proportion of patients with underlying rheumatologic causes of HLH (only 25%).
Notably, OS was 75% among the four-patient subgroup with rheumatologic triggers. Only two patients with a non-rheumatologic cause of HLH (2/12, 17%) survived follow-up. One of these two patients (patient #16) had no clearly evident trigger for secondary HLH, and this combined with his relatively young age suggests the possibility of occult primary HLH due to an unknown mutation which could not be identified on genetic testing (this patient subsequently underwent allogeneic bone marrow transplantation following anakinra-induced remission). The findings in this study, and those of the above cited studies, suggest that anakinra may have particular utility in those specific instances of secondary HLH which arise due to rheumatologic or autoimmune triggers (MAS). Anakinra does not appear to have nearly the same efficacy in secondary HLH due to other causes such as hematologic malignancy or infection. This may be due to the unique cytokine profile of MAS relative to other causes of secondary HLH, or may be due to the fact that the associated hematologic malignancies and infections simply have an intrinsically worse prognoses than rheumatologic disorders (independent of HLH). Notably, some studies have reported particularly good outcomes with intravenous rather than subcutaneous use of anakinra, and the optimal route of administration may merit further investigation [16, 19, 22, 23].

Anakinra was well-tolerated in this study as well as in all those cited above. This is an important distinction when comparing it to etoposide-based therapy, which may be highly toxic, immunosuppressive, and myelosuppressive [24, 25]. These immunosuppressive and myelosuppressive properties are challenges in cases of HLH due to hematologic malignancy (wherein patients may already be receiving or may need to subsequently receive additional immunosuppressive and myelosuppressive chemotherapy), infection (wherein immunosuppression and myelosuppression risk worsening the underlying infection), and rheumatologic disease (wherein patients are often already on multiple immunosuppressants, and the addition of etoposide may cause greater susceptibility to infection, and may limited use of other immunosuppressants due to myelosuppression). The non-myelosuppressive, and only mildly immunosuppressive, properties on anakinra make it relatively easier to combine with other therapies targeting the underlying triggers of secondary HLH.

This study is limited by its retrospective nature and small sample size (although it is the largest series describing the use of anakinra in adult secondary HLH reported to date). Patients received anakinra at different lines of therapy, with differing prior and concurrent therapies, at a wide variety of dosage schedules, and for varying periods of time. This heterogeneity of use across cases makes firm conclusions difficult, and limits any definitive statements regarding anakinra’s efficacy and toxicity. Clearly, prospective studies...
are needed (and even additional retrospective experiences which may add to the pool of available data would be useful). Nevertheless, it does appear that anakinra may be of significant utility in cases of secondary HLH due to rheumatologic causes (MAS), and likely of more limited utility in secondary HLH of other etiologies. Anakinra appears to be well tolerated with only rare and minimal toxicity. This is an important feature in the context of secondary HLH where the ability to combine HLH-directed therapies with therapies for the provoking disease process is crucial.

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Declarations

Conflict of interest  The author has no conflicts of interest to report.

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