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ORIGINAL ARTICLE

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 may 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.

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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 χ^2 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 therefor 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 started 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 χ^2 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 survival
Primary hematologic malignant etiology	1	65	F	myelofibrosis in blast phase, enterococcus bacteremia	5	206	109,988	Dexamethasone 40 mg daily, ruxolitinib 10 mg bid	Dexamethasone 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 viremia	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	Dexamethasone 20 mg daily, etoposide (part of ICE protocol)	Dexamethasone 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	Dexamethasone 20 mg daily, etoposide (past 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	6	229	79,812	Dexamethasone 40 mg daily, etoposide	dexamethasone 20 mg iv 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 survival
	11	64	M	COVID19 pneumonia, pseudomonal sepsis	6	199	36,291	Dexamethasone 20 mg daily	Dexamethasone 20 mg daily	Antibiotics	26	29	200 mg subq q8	12	None	No	0.5
Primary rheumatologic etiology	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	M	unknown	7	231	9346	Prednisone 90 mg daily, IVIG	Dexamethasone 20 mg daily	None	15	28	200 mg subq q8	31	None	Yes	49

CHOEP cyclophosphamide–hydroxyldaunorubicin–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	9011	10,524	11,071	9452	15,420	66,470	69,055		
	3	No	1.8	96%	131,063	91,139	22,450	12,909	6337	10,281	8367	9372	5628	9337	19,069
	4	Yes	57	79%	11,897	3771	3322	2532							239
	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%	4054	4604	4706	3167	6245	5121	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	4103	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%	1458	1385	1069	797	688	1222	1284	1965	1132		
	15	Yes	4	88%	88,905	49,508	24,428	13,883	10,475	10,389			12,720		
Other	16	Yes	49	72%	9346	7570	6606	5606	4879	3990	3395	3134	2534	2691	2595

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 provoking 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 etiologies), 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 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%).

Table 3 Previously described cohorts of adult secondary HLH patients treated with anakinra are summarized

Author, Year	N	Causes of HLH (%)	HLH-Directed Treatments	Outcomes
Dimopoulos, 2020 [22]	8	COVID-19 pneumonia/sepsis (100%)	Anakinra 200 mg IV q8, corticosteroids (dosage unspecified)	Five of 8 patients (63%) survived. This reported OS was higher than historical series of patients with sHLH in sepsis
Kumar, 2017 [18]	13	Autoimmune/rheumatologic (62%), hematologic malignancy (23%), unknown (8%), other (8%)	Anakinra 100 mg subq q12 (given with cyclosporine, IVIG, and corticosteroids in most instances)	Nine of 13 patients (69%) survived, including 7 of 8 (88%) with autoimmune/rheumatologic disease
Monteagudo, 2020 [19]	5	Autoimmune/rheumatologic (80%), unknown (20%), other	Continuous anakinra infusion (up to 2400 mg/d)	Four of 5 (80%) patients survived. Two patients had previously responded poorly to subq anakinra
Sammut, 2020 [20]	4	CMV viremia (25%), hematologic malignancy (25%), rheumatologic (25%), unknown (25%)	Anakinra 100 mg subq daily, with corticosteroids (75%), or with HLH-2004 protocol (25%)	Two of 4 (50%) patients survived
Wohlfarth, 2019 [21]	8	Unknown (38%), hematologic malignancy (25%), autoimmune disease (13%), EBV viremia (13%), other (13%)	Anakinra 100 m–200 mg q8, with IVIG (88%) and/or high-dose CS (62%)	Four of 8 patients (50%) survived hospitalization

CMV cytomegalovirus, *COVID19* coronavirus disease 2019, *CS* corticosteroid, *EBV* Epstein–barr virus, *HLH* hemophagocytic lymphohistiocytosis, *IV* intravenous, *sHLH* hemophagocytic lymphohistiocytosis, *subq* subcutaneous

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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