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Treatment with emapalumab in an ADA-SCID patient with refractory hemophagocytic lymphohistiocytosis-related graft failure and disseminated BCGitis

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Running heads: Treatment of HLH-related graft failure by emapalumab

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Interferon gamma (IFNγ)-targeted immunotherapy with emapalumab, a fully human monoclonal antibody, was recently approved by FDA for the treatment of adult and pediatric patients with primary hemophagocytic lymphohistiocytosis (HLH) who have refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.[1,2] Moreover, emapalumab has shown promising efficacy in the treatment of patients with graft failure (GF) requiring a second allogeneic hematopoietic stem cell transplantation (HSCT).[3] Interestingly, growing evidence supports common pathophysiolological mechanisms between HLH and immune-mediated GF, highlighting the key role of IFNγ in both conditions.[3]

IFNγ is a cytokine produced by macrophages and lymphocytes that plays a critical role in both innate and adaptive immune responses. In patients with complete IFNγ receptor deficiency or developing anti-IFNγ auto-antibodies, the absence of IFNγ biological activity leads to an increased susceptibility to specific infections, such as mycobacterial infections.[4,5] For this reason, latent tubercolosis (TB) infection represented an exclusion criterion in clinical trials investigating the therapeutic role of emapalumab in primary (NCT03312751; NCT01818492) and secondary HLH (NCT03311854).

Herein, we report a case of secondary HLH-related GF in the context of HLA-haploidentical HSCT treated with emapalumab in the presence of concomitant life-threatening infections including disseminated BCGitis.

The patient is a 4 years old girl with Severe Combined Immunodeficiency caused by Adenosine Deaminase Deficiency (ADA-SCID) referred to our institution for ex-vivo hematopoietic stem cell (HSC)-gene therapy (GT) with Strimvelis® in the absence of a human leukocyte antigen (HLA)-identical sibling donor.[6] She presented in poor clinical conditions with bilateral abscesses on lower limbs, corresponding to the sites of Polyethylene glycol-modified adenosine deaminase (PEG-ADA) injections (Figure 1A). Presence of *Mycobacterium bovis* was identified by direct Next Generation Sequencing performed on the material drained from the limb abscesses using the Deeplex® Myc-TB, an all-in-one test for species-level identification, genotyping and prediction of antibiotic resistance in *Mycobacterium tuberculosis* complex. Results were further confirmed by standard mycobacteriology procedure and Whole Genome Sequencing of the strain. Moreover, magnetic resonance imaging (MRI) documented an intracerebral granuloma (Figure 1C) and vertebral osteolytic lesions, that, along with the limb abscesses, led to the diagnosis of disseminated BCGitis, as reactivation of the BCG vaccine strain received at birth. She was treated with surgical incision of the abscesses and anti-TB treatment [4-drug regimen (isoniazid, rifampicin, ethambutol, moxifloxacin) for 12 months as intensive phase, 2-drug regimen (isoniazid, rifampicin) for 6 months as continuation phase]. After 7 months of anti-TB treatment, at resolution

of cutaneous abscesses and with residual encephalic mycobacterial lesions, the patient was considered eligible and treated with Strimvelis®. Failure of engraftment of gene-corrected HSC was declared at d+90 and enzyme replacement therapy (ERT) was resumed.

Subsequently, due to the lack of a matched unrelated donor and after ERT withdrawal, the patient received a first HLA-haploidentical HSCT after $\alpha\beta^+$ T-cell and $CD19^+$ B-cell depletion (TCD) from the father after reduced toxicity conditioning regimen (Table 1).[7] However, HSCT failed due to primary GF likely related to concomitant adenovirus reactivation in the peri-engraftment phase. A second paternal haplo-HSCT was performed after reduced intensity conditioning employing exceeding HSC cryopreserved from the first transplant and infused on d+31 post first HSCT (Table 1). On d+13 after the second haplo-HSCT, the patient showed persistent fever, hepatosplenomegaly, high levels of triglycerides (383 mg/dL) and markedly elevated inflammatory markers such as ferritin (18000 mg/dl) and soluble IL2 receptor (16809 pg/ml; reference values 600-2000) (Figure 2A,B). Donor chimerism on both peripheral blood (PB) and bone marrow (BM) was documented on day+10 and +13, respectively; however, it was followed by secondary GF with complete loss of donor engraftment (day+18). BM morphology showed hypocellularity with features of active hemophagocytosis. A secondary HLH was diagnosed based on 6 out of 8 HLH-2004 criteria,[8] likely triggered by concurrent infections, including *Stenotrophomonas maltophilia* bacteremia, invasive pulmonary aspergillosis (Figure 1E) and adenovirus reactivation. Treatment with methylprednisolone (2 mg/Kg/day) and high dose immunoglobulins was started.

In order to control HLH and reduce the possibility of GF after a third HSCT, emapalumab compassionate use was requested and approved for this severely immunocompromised patient unable to tolerate standard HLH immunochemotherapy.

At time of emapalumab initiation, adenovirus reactivation and invasive pulmonary aspergillosis were active: adenovirus was detected both in plasma and stool with 1940 copies/ml and >1000000 copies/ml, respectively; while galactomannan levels were above the upper limit of detection (index>6). Intensive antimicrobial treatment included antivirals (intravenous cidofovir, later switched to oral brincidofovir) and antifungals (voriconazole plus anidulafungin, later switched to liposomial amphotericine-B plus anidulafungin to minimize drugs interactions). Conversely, rifampicin and isoniazid were continued as secondary prophylaxis to avoid the risk of TB reactivation of TB, which was regularly monitored through blood cultures, fecal PCR for *Mycobacterium bovis* and brain MRI. Emapalumab was administered intravenously twice a week for a total of 15 infusions with the objective to taper glucocorticoids promptly. After the first dose at 1mg/kg, emapalumab dose was increased to 3mg/kg: the laboratory parameters, while not

worsening, did not show a satisfactory improvement. Thereafter, emapalumab dose was increased to 6mg/kg, based on deterioration of inflammatory parameters (e.g. ferritin, CRP) (Figure 2A). IFNγ levels were not particularly elevated in this patient, as documented by CXCL9 values around 260 pg/mL at start of emapalumab treatment (Figure 2B). Nonetheless, the pharmacokinetics (PK) of emapalumab (Figure 2C) was affected by target mediated drug disposition, documenting high IFNγ production and requiring emapalumab dose increase. CXCL9 progressively decreased to levels below 80 pg/mL, documenting complete neutralization of IFNγ. By the time of the third haplo-HSCT, the dose of glucocorticoids was reduced to approximately 50% of the starting dose, while maintaining a good clinical control of HLH. The patient, despite the occasional temporary worsening of a few HLH laboratory parameters, did not progress into overt HLH, likely due to the neutralization of IFNγ.

The patient received the third TCD haplo-HSCT from the mother after a total of 6 emapalumab doses. Conditioning regimen included chemotherapeutic agents active against HLH,[8] while cyclosporin-A (Cs-A) was added for graft-rejection prevention (Table 1). Anti-HLA antibodies were undetectable before and after HSCT. Neutrophil and platelet engraftment occurred on d+10 and d+14, respectively. BM aspirate at d+21 was normo-cellulated with no evidence of hemophagocytosis and showed full donor chimerism. Emapalumab was administered until achievement of sustained donor engraftment (d+28) (Figure 1G). No adverse events occurred. HLH clinical and laboratory parameters progressively improved (Figure 2A,B) allowing Cs-A and steroids tapering and ultimately discontinuation (d+36 and d+59, respectively) (Figure 1G).

Remarkably, during blockade of IFN-γ with emapalumab, infections remained stable or improved with antimicrobial medications. At the end of treatment, the cutaneous TB lesions did not show any reactivation (Figure 1B) and the brain imaging showed improvement of the lesions documented prior to emapalumab (Figure 1D). Bacteremia resolved and invasive pulmonary aspergillosis improved with favorable radiological evolution (Figure 1F) and reduction of galactomannan up to negativity at day +132 post-HSCT. After 8-week treatment with emapalumab, at d+39 post HSCT, adenovirus became undetectable in plasma. Treatment with brincidofovir was continued until negativity also in stool and therefore withdrawn one month later. At d+100 post-HSCT the patient was clinically well with full donor chimerism on total BM and PB, as well as on lymphoid and myeloid subpopulations (Table 1). She is currently 9 months after the third haplo-HSCT and remains in good clinical conditions and infection-free. Based on emapalumab half-life, the patient has remained on anti-TB prophylaxis to mitigate the risk of reactivation until measurable levels of the drug were present.

In conclusion, we report the case of a very fragile, heavily immunosuppressed patient affected by ADA-SCID who experienced GF after multiple HSCT in the presence of life-threatening infections including disseminated TB, who was safely treated with emapalumab.

The activation of IFNγ pathway has a well-documented double role both in controlling mycobacterial infections and, also, in sustaining HLH hyperinflammatory response.[10,11] In our patient we had to face both challenges: on one side to prevent TB reactivation and on the other to inhibit the hyperinflammation responsible for both HLH and GF.

Upon review of emapalumab safety and efficacy data reported in primary[2,12,13] and secondary HLH,[14] and despite the potential risk of TB reactivation, the benefit/risk ratio of treating with emapalumab was deemed favorable. Interestingly, during emapalumab treatment, the known TB abscesses remained inactive and the brain TB findings improved. In this context, neutralization of IFNγ might have contributed to control HLH without the prolonged use of additional myelosuppressive drugs. Moreover, since a third GF was not observed, our findings suggest that, in association with other lines of immunosuppressive/chemotherapic agents, emapalumab might have played a role in reducing the risk of graft rejection, as already shown in both murine models and humans.[3,15,16] In addition, while an intrinsic defect of the mesenchymal/osteblast compartment in ADA-SCID patients with reduced capacity to support *in vitro* and *in vivo* hematopoiesis[9] may have contributed to the repeated GFs; the concomitant use of Cs-A in the peri-transplant phase and the mega-dose of $CD34^+$ cells infused after the third haplo-HSCT may have played a role in preventing rejection.

This seminal case suggests the feasibility and safety of emapalumab administration to manage secondary HLH and repeated GF also in patients bearing multiple active infections, including TB.

Authorship contributions

Contribution: FT, VG followed the clinical course of the patient, collected data, analyzed results and wrote the paper; FB, FF, MM, VC, MD, MPC, ESF, CO followed the clinical course of the patient and collected data; ZK and SG followed the patient before referral to our Institution; SG collected peripheral blood hematopoietic stem cells from the donors; MZ, CP and RM performed graft manipulation; BM performed chimerism analyses; CB and MB performed radiological evaluations; DMC performed fecal PCR for detection of Mycobacterium bovis; VA and CDM provided emapalumab as per CU, performed PK/PD emapalumab evaluations, critically read the manuscript and helped with scientific discussion; AA and FC critically revised the manuscript and

helped with scientific discussion; MEB advised on the design the study, analyzed data and contributed to the final writing of the paper.

Disclosure of conflict of interest

MPC is PI of the long-term follow up study sponsored by Orchard Therapeutics for patients treated with Strimvelis and AA is PI of clinical trials sponsored by Orchard Therapeutics. VA is an employee of Sobi; CdM is consultant for Sobi.

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References

1. Al-Salama ZT. Emapalumab: First Global Approval. Drugs. 2019;79(1):99-103.
2. Locatelli F, MB Jordan MB, Allen C, et al. Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis. N Engl J Med. 2020;382(19):1811-1822.
3. Merli P, Caruana I, De Vito R, et al. Role of interferon-γ in immune-mediated graft failure after allogeneic hematopoietic stem cell transplantation. Haematologica. 2019;104(11):2314-2323.
4. Dorman SE, Picard C, Lammas D, et al. Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. Lancet. 2004;364(9451):2113-2121.
5. Lammas DA, Casanova JL, Kumararatne DS. Clinical consequences of defects in the IL-12-dependent interferon-gamma (IFN-gamma) pathway. Clin Exp Immunol. 2000;121(3):417-425.
6. Kohn DB, Hershfield MS, Puck JM, et al. Consensus approach for the management of severe combined immune deficiency caused by adenosine deaminase deficiency. J Allergy Clin Immunol. 2019;143(3):852-863.
7. Bertaina A, Merli P, Rutella S, et a. HLA-haploidentical stem cell transplantation after removal of αβ+ T and B cells in children with nonmalignant disorders. Blood. 2014;124(5):822-826.
8. Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-131.
9. Sauer AV, Mrak E, Jofra Hernandez R, et al. ADA-deficient SCID is associated with a specific microenvironment and bone phenotype characterized by RANKL/OPG imbalance and osteoblast insufficiency. Blood. 2009;114(15):3216-3226.
10. Zhang SY, Boisson-Dupuis S, Chapgier A, et al. Inborn errors of interferon (IFN)-mediated immunity in humans: insights into the respective roles of IFN-alpha/beta, IFN-gamma, and IFN-lambda in host defense. Immunol Rev. 2008;226:29-40.
11. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood. 2004;104(3):735-743.
12. Locatelli F, Jordan MB, Allen CE, et al. Safety and efficacy of emapalumab in pediatric patients with primary hemophagocytic lymphohistiocytosis. Blood. 2018;132(Supplement 1):LBA-6.
13. De Benedetti F, Brogan P, Grom P, et al. Emapalumab, an interferon gamma (IFNγ) blocking monoclonal antibody, in patients with Macrophage Activation Syndrome (MAS) complicating systemic Juvenile Idiopathic Arthritis (sJIA). Annals of Rheumatic Diseases. 2019;78 (Supplement 2):178.
14. Lounder DT, Bin Q, de Min C, Jordan MB. Treatment of refractory hemophagocytic lymphohistiocytosis with emapalumab despite severe concurrent infections. Blood Adv. 2019;3(1):47-50.

15. Prencipe G, Caiello I, Pascarella A, et al. Neutralization of IFN-γ reverts clinical and laboratory features in a mouse model of macrophage activation syndrome. J Allergy Clin Immunol. 2018;141(4):1439-1449.
16. Buatois V, Chatel L, Cons L, et al. Use of a mouse model to identify a blood biomarker for IFNγ activity in pediatric secondary hemophagocytic lymphohistiocytosis. Transl Res. 2017;180:37-52.

Table 1. Characteristics of the 3 HLA-haploidentical HSCT performed.

	I	**II**	**III**
Donor	Father	Father	Mother
Conditioning regimen	Treosulfan 14 g/m^2 (days -6, -5, -4); Fludarabin 40 mg/m^2 (days -6, -5, -4, -3); ATG Grafalon 4 mg/kg (days -5, -4, -3); Rituximab 200 mg/m^2 (day-1)	Fludarabine 30 mg/m^2 (days -5;-4,-3); Cyclophosphamide 500 mg/m^2 (days -5, -4, -3); ATG Thymoglobulin 2 mg/kg (days -3, -2); Rituximab 200 mg/m^2 (day -1)	VP-16 150 mg/m^2 (days -5,-4,-3); Cyclophosphamide 500 mg/m^2 (days -5,-4,-3); ATG Grafalon 2 mg/Kg (days -3, -2) Cyclosporine-A 3 mg/kg (from day -2 to +36)
GvHD prophylaxis	TCD	TCD	TCD
Cell dose			
CD34$^+$ cells, $\times10^6$/kg	9.52	10.5	- $\alpha\beta^+$CD19$^+$-depleted CD34$^+$=8.09; - positively selected CD34$^+$=15.01 Total CD34$^+$ =23.1
TCR-$\alpha\beta^+$ CD3$^+$ $\times10^4$/kg	9	10	9
TCR-$\gamma\delta^+$ CD3$^+$, $\times10^6$/kg	13.1	14.6	6.7
CD20$^+$ $\times10^4$/kg	12	13	9
CD3$^-$CD19$^-$CD20$^-$, $\times10^6$/kg	**37**	**41**	**13**
Engraftment's kinetic			
Neutrophils*	NA	NA	+10 days
Platelets**	NA	NA	+14 days
PB Chimerism#	-	Donor >90% (day +10)§	2nd donor 86%; host 1.2%; 1st donor absent (father) (day +12)
		Donor >70% (day +13)§	
		Host >90% (day +18)§	
		Donor 0%; host >99% (day +28)	2nd donor 89%; host 0.4%; 1st donor absent (father) (day +18)
			2nd donor >95%; host 0%; 1st donor absent (father) (day +100)
BM Chimerism	Donor 0% (day +20)	Donor >70%; host 2.3% (day +13)	2nd donor >99%; host 0.7%; 1st donor absent (father) (day +21)
		Donor 0%; host >99% (day +20)	2nd donor >90%; host 0%; (day +100)

Table legend: ATG: anti-thymocyte globulin; GvHD: Graft-versus-Host Disease; TCD: T-cell depletion; TCR: T-cell receptor; NA: not achieved; PB: peripheral blood; BM: bone marrow. Haploidentical donors were mobilized with G-CSF (father) and G-CSF + Plerixafor (mother).

*Defined as the time needed to reach an absolute neutrophil count ≥0.5 x 10^9 per liter.

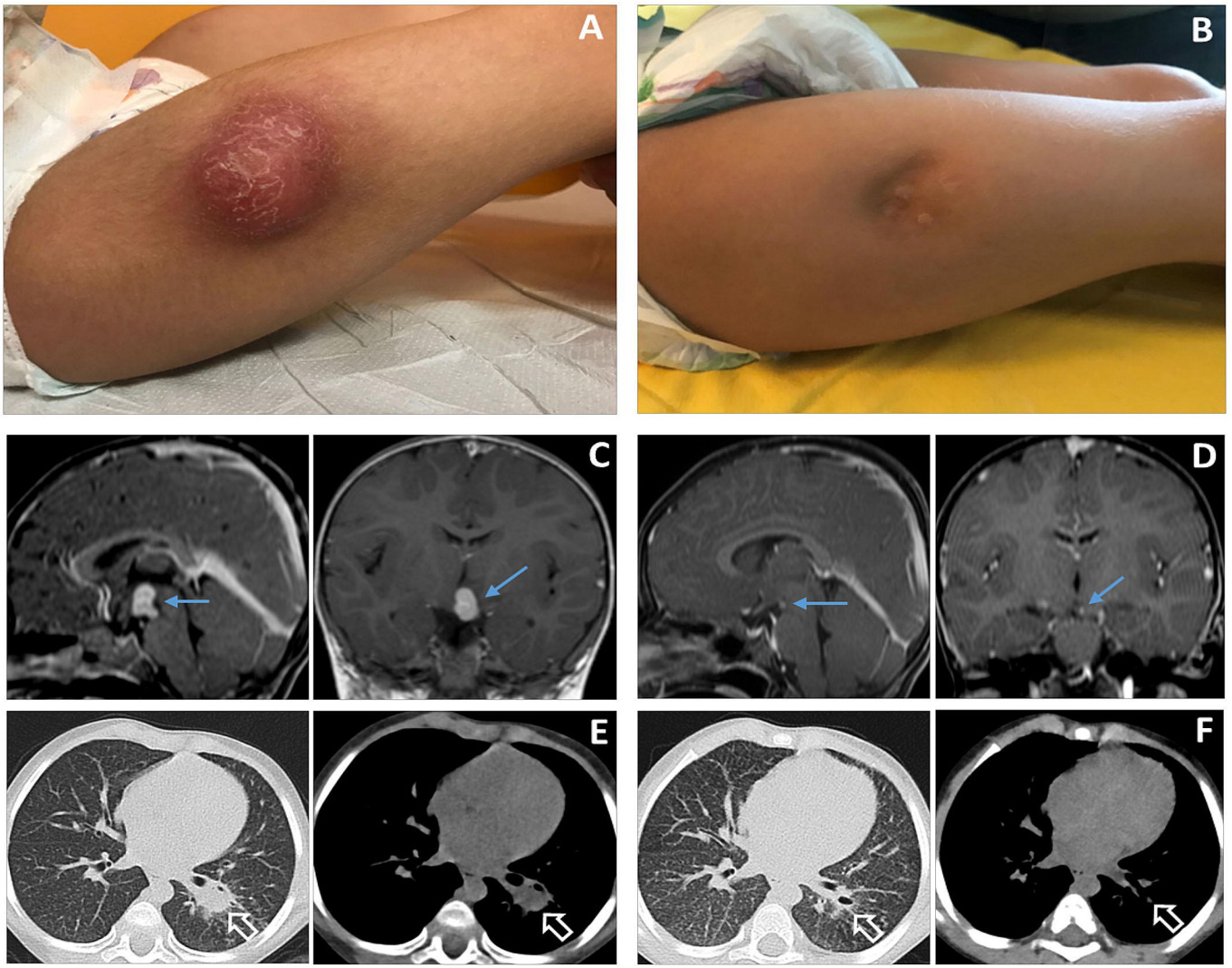
**Defined as the time needed to reach an unsupported platelet count ≥20 x 10^9 per liter.

Primary graft failure was defined as: ANC <0.5 × 10^9/L by day +28; Hemoglobin <80 g/L and platelets <20 × 10^9/L; Cord blood transplantation: up to day +42. Secondary graft failure was defined as: ANC <0.5 × 10^9/L after initial engraftment not related to relapse, infection, or drug toxicity.

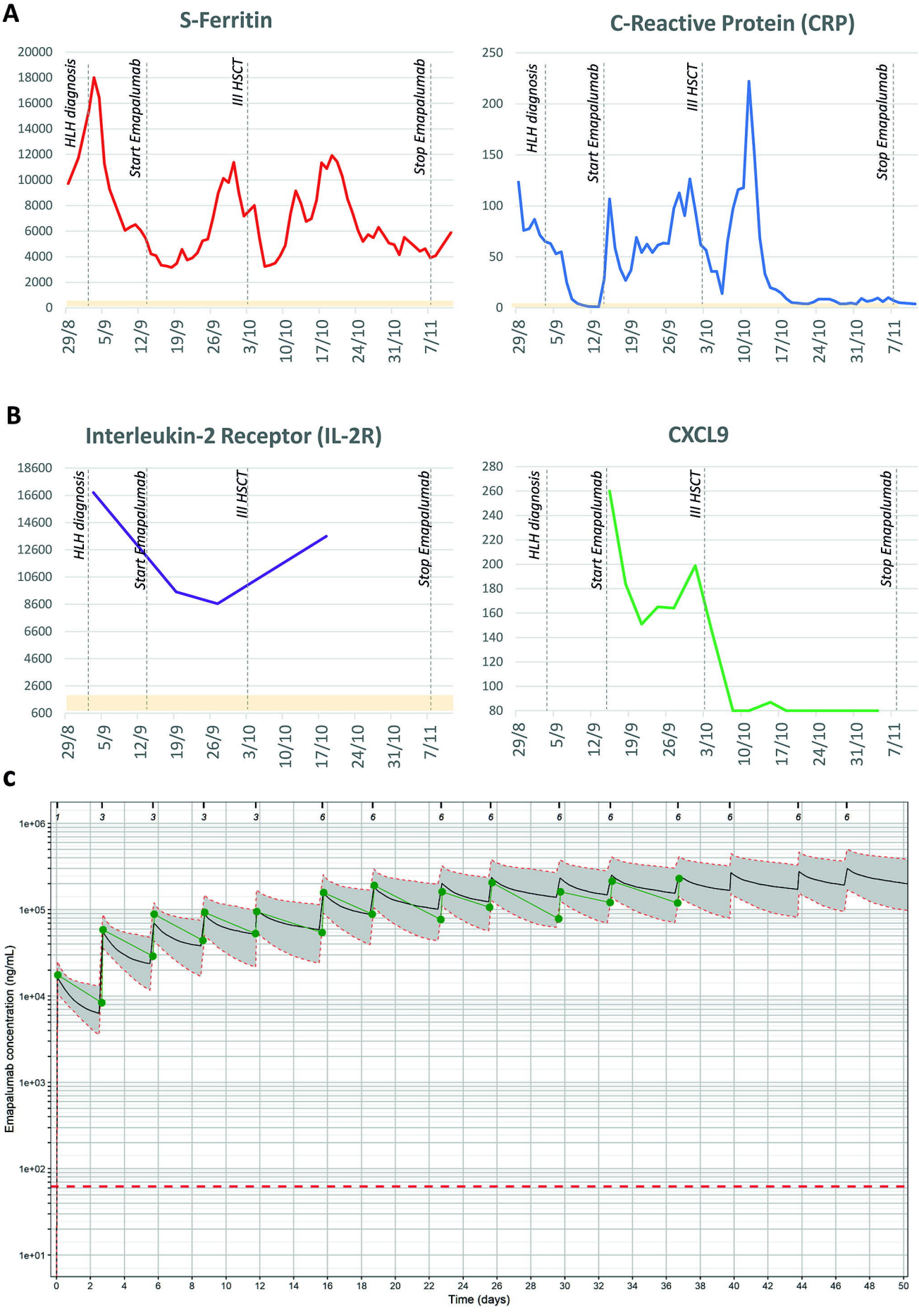
#Chimerism was assessed on total and/or sorted PB and BM aspirate samples by Real Time PCR and Relative Quantification. At d+100 after the third haplo-HSCT chimerism analysis was performed also on PB lymphoid and myeloid subpopulations including $CD3^+$ (>90%), $CD15^+$ (>90%) and $CD14^+$ (>85%) cells.
§Presence of host/donor cells not evaluated due to insufficient material

Figure 1. Clinical, brain MRI and chest CT images of TB and fungal infections, and schematic summary of treatments. (A) Localized abscesses on lower limbs at the sites of PEG-ADA injection before surgical incision. (B) Localized abscesses on lower limbs at d+100 after the third haplo-HSCT. Surgical incision was performed before HSC-GT. (C) Brain MRI at diagnosis of intracerebral TB granuloma. Sagittal and coronal post-contrast T1W brain MRI images show a hypothalamic contrast enhancing lesion suggestive for tuberculous granuloma. (D) Brain MRI at d+100 after the third haplo-HSCT showing marked reduction of the tuberculous granuloma. (E) CT images of the lungs at time of aspergillosis diagnosis after the second haplo-HSCT. Axial chest CT images with lung window (on the left) and mediastinal window (on the right) show a left lower lobe pulmonary mass compatible with pulmonary aspergillosis. (F) CT images of the lungs at d+100 after the third haplo-HSCT showing marked improvement. (G) Schematic representation of the treatment given before and during the third haplo-HSCT to control secondary HLH and prevent GF. MPD: methylprednisolone; VP-16: etoposide; CTX: cyclophosphamide; ATG: anti-tymocyte globulin; Cs-A: cyclosporin-A; HSCT: hematopoietic stem cells transplantation.

Figure 2. Significant inflammatory markers from the HLH diagnosis up to the end of treatment with emapalumab and pharmacokinetics (PK) of the drug. (A) Serum ferritin [normal values (nv): 15-150 ng/ml] and CRP (nv <6 mg/L); trends are reported in red and blue lines, respectively. (B) IL2 receptor (nv 600-2000 pg/ml) and CXCL9 levels are reported in purple and green, respectively. Normal ranges are reported in light yellow. (C) Concentration-time profile of emapalumab in the patient. Green dots and solid lines represent observed emapalumab concentrations. Black solid lines represent simulated concentrations for the specific patient (i.e. taking into consideration the dosage schedule and measured total IFNγ concentrations) based on the population pharmacokinetic model of emapalumab in HLH patients. The grey area surrounded by orange dotted lines represents the 90% prediction interval of the simulated concentrations. The dotted red line represents the limit of quantification of the bioanalytical assay (62.5 ng/mL). The ticks and the numbers on the top line represent times of administration and dose in mg/kg.
CRP: C Reactive Protein; IL2: Interleukin 2; CXCL9: Chemokine (C-X-C motif) ligand 9; IFNγ: Interferon gamma.



Tucci F et al., Figure 1


A
S-Ferritin
C-Reactive Protein (CRP)
HLH diagnosis
Start Emapalumab
III HSCT
Stop Emapalumab
B
Interleukin-2 Receptor (IL-2R)
CXCL9
C
Emapalumab concentration (ng/mL)
Time (days)