Colony-stimulating factors for the treatment of the hematopoietic component of the acute radiation syndrome (H-ARS): A review

Vijay K. Singh, Victoria L. Newman, Thomas M. Seed

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A B S T R A C T

One of the greatest national security threats to the United States is the detonation of an improvised nuclear device or a radiological dispersal device in a heavily populated area. As such, this type of security threat is considered to be of relatively low risk, but one that would have an extraordinary high impact on health and well-being of the US citizenry. Psychological counseling and medical assessments would be necessary for all those significantly impacted by the nuclear/radiological event. Direct medical interventions would be necessary for all those individuals who had received substantial radiation exposures (e.g., >1 Gy). Although no drugs or products have yet been specifically approved by the United States Food and Drug Administration (US FDA) to treat the effects of acute radiation syndrome (ARS), granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), and pegylated G-CSF have been used off label for treating radiation accident victims. Recent threats of terrorist attacks using nuclear or radiologic devices makes it imperative that the medical community have up-to-date information and a clear understanding of treatment protocols using therapeutically effective recombinant growth factors and cytokines such as G-CSF and GM-CSF for patients exposed to injurious doses of ionizing radiation. Based on limited human studies with underlying biology, we see that the recombinants, G-CSF and GM-CSF appear to have modest, but significant medicinal value in treating radiation accident victims. In the near future, the US FDA may approve G-CSF and GM-CSF as 'Emergency Use Authorization' (EUA) for managing radiation-induced aplasia, an ARS-related pathology. In this article, we review the status of growth factors for the treatment of radiological/nuclear accident victims.

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1. Introduction

Acute radiation syndrome (ARS) occurs in humans following whole-body or significant partial-body exposures to ionizing radiation with doses greater than 1 Gy, delivered at relatively high rates. Clinical components of ARS include the hematopoietic sub-syndrome (H-ARS, 2–6 Gy), gastrointestinal sub-syndrome (GIS; 6–8 Gy), and the cerebrovascular (>8 Gy) sub-syndrome [1]. However, these “sub-syndromes” tend to oversimplify the clinical reality of ARS as it often involves complex, multi-organ dysfunctions [2–4]. The cerebrovascular sub-syndrome is considered incurable, whereas, individuals receiving lower radiation doses that result in either the H-ARS alone or in combination with GIS, are more likely to be amenable to countermeasures. Therefore, the latter two sub-syndromes are specific targets for the development of novel therapeutics. This is particularly the case in terms of H-ARS, that is largely driven by the radiation-induced loss of vital, growth factor-modulated hematopoietic progenitors and, in turn, by massive losses of circulating, functions blood cells, i.e., the blood cytopenias.

Colony-stimulating factors are endogenous glycoproteins that induce bone marrow hematopoietic progenitors to proliferate and differentiate into specific mature blood cell types [5,6]. Granulocyte colony-stimulating factor (G-CSF) is a lineage specific colony-stimulating factor produced by monocytes, fibroblasts, and endothelial cells. It regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation.
analogs of G-CSF have been reported (Biograstim\textsuperscript{a}, Filgrastim \textsuperscript{b}, Ratiopharm/Ratiograstim\textsuperscript{a}, Tevagrastim\textsuperscript{a} (XM02); Zarzio\textsuperscript{c} and Nivestim\textsuperscript{d})\textsuperscript{14}. It acts by binding to a G-CSF-specific transmembrane receptor (belonging to the class I cytokine receptor family), which are expressed on various hematopoietic cells such as stem cells, multi-potential progenitors, myeloid-committed progenitors, neutrophils, and monocytes. The receptor forms homo-oligomeric complexes upon ligand binding. Its mode of action and role in differentiation/maturation of cells are graphically represented in Fig. 1. It has been approved for the following clinical indications: (a) cancer patients receiving myelosuppressive chemotherapy, (b) patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, (c) cancer patients receiving bone marrow transplants (BMT), (d) patients undergoing peripheral blood progenitor cell collection and therapy, (e) patients with severe chronic neutropenia.

Tbo-filgrastim (a short-acting recombinant non-glycosylated, bio-similar form of G-CSF, Tevagrastim\textsuperscript{a}), Teva Pharmaceutical Industries Ltd., Israel/Sicor Biotech UAB, Vilnius, Lithuania, also known as XM02) was granted United States Food and Drug Administration (US FDA) approval on 29 August 2012 to help reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia\textsuperscript{15}. Although both tbo-filgrastim and filgrastim (Neupogen\textsuperscript{c}, Amgen Inc., Thousand Oaks, CA, USA) have a structure containing 175 amino acids and are produced through recombinant DNA technology in the Escherichia coli bacteria, they have different formulations\textsuperscript{16}. The sponsor for tbo-filgrastim, Teva Pharmaceuticals, rather than following the abbreviated pathway for bio-similar compounds and relying on clinical efficacy and safety data for filgrastim, submitted a full biological licensing application (BLA) with clinical efficacy and safety data obtained from studies with tbo-filgrastim to the FDA for approval (the abbreviated pathway was not available with the US FDA at the time of submission). The indication, for which tbo-filgrastim was approved, is narrower than those for filgrastim based on the clinical data included in the biological licensing application. The US FDA does not consider tbo-filgrastim to be bio-similar to or interchangeable with filgrastim\textsuperscript{15}.

Another US FDA-approved product is pegfilgrastim (pegylated G-CSF: Neulasta\textsuperscript{e}, Amgen Inc.), a sustained-duration form of filgrastim. It consists of the filgrastim molecule with a 20 kDa monomethoxypolyethylene glycol molecule covalently bound to the N-terminal methionyl residue for an average molecular weight of approximately 39 kDa\textsuperscript{17}. The biological activity and mechanism of action of the pegylated and non-pegylated forms are identical so clinical requirements determine which form will be used\textsuperscript{18}. Pegfilgrastim, administered to cancer patients undergoing treatment, is typically injected once, 24 h after each cycle of high-dose chemotherapy and no sooner than 14 days before the next chemotherapy treatment. Filgrastim is typically injected on a daily basis until neutrophil counts come back to normal levels.

GM-CSF, like G-CSF, is a hematopoietic growth factor that stimulates proliferation and differentiation of hematopoietic progenitor cells. GM-CSF can activate mature granulocytes and macrophages and is able to induce partially committed progenitor cells in the granulocyte–macrophage pathways to divide and differentiate. Functional cells later in this differentiation pathway include neutrophils, monocytes/macrophages and myeloid- derived dendritic cells. Additionally, GM-CSF is a bi-lineage factor able to affect the myelomonocytic lineage in a dose-dependent manner and can promote the proliferation of not only progenitors committed to granulocyte and monocyte production, but also a limited capacity to stimulate megakaryocytic and erythroid progenitors as well, although other factors are required to induce complete maturation of the latter two lineages\textsuperscript{19}. The species-specific biological activity and various cellular responses (i.e., division, maturation, activation) are induced through GM-CSF binding to specific receptors expressed on the cell surface of target cells\textsuperscript{20}. It has been approved for use, by the US FDA, for the following clinical indications: (a) neutrophil recovery following chemotherapy in acute myelogenous leukemia, (b) mobilization of peripheral blood progenitor cells, (c) post peripheral blood progenitor cell transplantation, (d) myeloid reconstitution after autologous or allogeneic BMT, (e) BMT failure or engraftment delay.

Currently, there are four recombinant leukocyte growth factors with BLA approval: BLA 103353, Neupogen\textsuperscript{c} (filgrastim, Amgen, Inc.), BLA 125031, Neulasta\textsuperscript{e} (pegfilgrastim, Amgen, Inc.), BLA 103362, Leukine\textsuperscript{f} (sargramostim, Genzyme Inc., Cambridge, MA, USA) and BLA 125294, TBO-Filgrastim\textsuperscript{b} (tbo-filgrastim, Sicor Biotech, UAB)\textsuperscript{21}. The use of growth factors in treating victims in a radiation-exposure scenario is rationalized based on the following three facts: (a) improved survival in irradiated animals (mice, canines, minipigs, and NHPs), (b) improved neutrophil recovery in cancer patients-treated with growth factors, and (c) an observed diminished period of neutropenia in a limited number of radiation accident victims treated with filgrastim and sargramostim\textsuperscript{22}. The limited clinical data available regarding these growth factors validate their biological response. However, the problem with this limited data is the manner in which these recombinants have been administered; in almost all cases, administration was delayed, under varying conditions, making the CSF's role in recovery difficult to determine definitively.

The US emergency use authorization (EUA) is a critical new tool for the medical and public health communities. It is applicable for both civilian and military use, as it fills the need for timely and practical medical treatment in emergency situations. The Project BioShield Act of 2004, among other provisions, established the comprehensive EUA program. EUA permits the US FDA to approve the emergency off-label use of products approved for other indications or the use of drugs, devices, and medical products holding no prior approval, clearance, or licensing by FDA. Prior to the establishment of the EUA, the sole mechanism for making unapproved products available in an emergency situation, was through obtaining Investigational New Drug (IND) status.

On the 3rd of May, 2013, the US FDA Center for Drug Evaluation and Research convened a joint meeting of the Medical Imaging Drugs Advisory Committee and the Oncologic Drug Advisory Committee to discuss the safety and efficacy of currently approved leucocyte growth factors as potential treatments for radiation-induced myelosuppression associated with a radiological/nuclear incident. During this meeting the committee considered the known filgrastim effects in the chemotherapy setting, as well as comparable filgrastim effects in severely myelosuppressed humans exposed acutely to ionizing radiation following a radiological/nuclear incident. Members voted in overwhelming support (17:1) of the concept that recombinant human G-CSF (rhG-CSF) would likely to produce significant clinical benefit in humans exposed unwantedly to radiation as a consequence of a given radiation accident\textsuperscript{23}.

In light of the above mentioned US FDA meeting and related events, we have tried here in this brief review to elaborate on recent preclinical and clinical developments associated with these leukocyte growth factors and to provide the information available on their therapeutic use and potentials in medically managing the hematopoietic component of ARS.
2. Promising radiation countermeasures stimulating G-CSF production

In the recent past, we have demonstrated that high levels of G-CSF are induced in mice by the administration of several promising radiation countermeasures that are currently under development. These new countermeasures include agents such as 5-androstenediol (5-AED/Neumune®) [24,25], CBLB502 (truncated flagellin: Entolimod™) [26], CBLB612 and CBLB613 (both lipopeptides of mycoplasma origin) [27,28], vitamin E isomers and their derivatives (α-tocotrienol [29,30], γ-tocotrienol [31], and α-tocopherol succinate [32,33]). Further, we have demonstrated in mice, that the administration of a G-CSF antibody completely abrogates the radioprotective efficacy of some radiation countermeasures (e.g., 5-androstenediol (5-AED/Neumune®) [24,25], CBLB502 (truncated flagellin: Entolimod™) [26], CBLB612 and CBLB613 (both lipopeptides of mycoplasma origin) [27,28], vitamin E isomers and their derivatives (α-tocotrienol [29,30], γ-tocotrienol [31], and α-tocopherol succinate [32,33]). Further, we have demonstrated in mice, that the administration of a G-CSF antibody completely abrogates the radioprotective efficacy of some radiation countermeasures (e.g.,

Fig. 1. Binding, signal transduction and role of G-CSF in hematopoietic cell maturation/differentiation. G-CSF binds to its transmembrane receptor (G-CSFR), and initiates a signaling cascade by phosphorylating/activating Janus kinase 2 (JAK-2). The activated JAK-2 can then initiate many signaling pathways, three of which are described here in abbreviated form. Each portrayed pathway is involved in stimulating cell proliferation, cell differentiation or the inhibition of apoptosis, indicated by the pink, green and blue colored signals, respectively. Green arrows indicate stimulation and red arrows indicate inhibition. Self-replacing hematopoietic cells give rise to multi-potent stem cells, which in turn give rise to lymphoid progenitors, erythroid progenitors, megakaryocytes, basophil progenitors, eosinophil progenitors or granulocyte–monocyte progenitors. Erythroid, megakaryocyte, basophil, eosinophil progenitors give rise to erythrocytes, platelets, basophils and eosinophils, respectively. Granulocyte–monocyte progenitors give rise to neutrophils and monocytes by stimulation with G-CSF with additional cytokines and growth factors such as IL-3, GM-CSF, and M-CSF. (STAT – signal transducer and activator of transcription, STAT5 – transcription factor of 5B, STAT3 – transcription factor of 3, P indicates phosphorylated or activated signal, RAS – Rat Sarcoma, RAF – rapid accelerated fibrosarcoma – extracellular-signal-regulated kinase 5, PI3K – phosphatidylinositol-4,5-bisphosphate 3-kinase (phophatidylinositide 3-kinases), BAD – Bcl-2 associated death promoter, BCL-xl – B-cell lymphoma-extra-large, CASPASES – cysteine-aspartic proteases AKA cysteine-dependent aspartate-directed proteases, PDK – pyruvate dehydrogenase kinase, Akt – protein kinase B, a serine/threonine-specific protein kinase, Bcl-2 – an anti-apoptotic protein, CIAP2 – Baculoviral IAP repeat-containing protein 3).
5-AED [34], CBLB502 [26], δ-tocotrienol [29], γ-tocotrienol [31], and α-tocopherol succinate [33,35], clearly suggesting that G-CSF, plays an important role in the radioprotective efficacy of these countermeasures. Recently, G-CSF and interleukin-6 (IL-6) have been identified as candidate biomarkers for the radioprotective and radiomitigative efficacy of CBLB502. Induction of both G-CSF and IL-6 by CBLB502 is toll-like receptor 5-dependent, dose-dependent within its efficacious dose range in both unirradiated and irradiated mammals (including rodents, canines, and NHPs), with both factors deemed critically important for CBLB502’s efficacy in increasing the survival of acutely irradiated animals [26]. These biomarkers may be useful for accurately predicting the dose of CBLB502 required to provide sufficient levels of radioprotection or radiomitigation in radiation-injured humans.

Other investigators also have reported stimulation of G-CSF by potential radiation countermeasures in mice. Meloxicam (a selective inhibitor of cyclooxygenase-2) protected mice against γ-radiation exposure and stimulated high levels of G-CSF when administered intraperitoneally (ip) [36–39]. Bar-Yehuda et al. have demonstrated stimulation of G-CSF by oral administration of CF101 (a myeloprotective synthetic agonist to the A3 adenosine receptor) by upregulation of phosphoinositide 3-kinase/nuclear factor-κB in mice [40]. Maitake beta-glucan (MD-fraction, polysaccharide derived from *Grifola frondosa*) stimulated G-CSF in granulocytic mice when administered ip, and subsequently, enhanced both granulopoiesis and the mobilization of granulocytes and their progenitors [41].

In acutely irradiated mice, maximal peripheral blood levels of G-CSF occur approximately 8 h after radiation exposure [42–44]. A second peak of G-CSF occurs around 12 days after 9.2 Gy radiation exposure (60Co) in CD2F1 mice [42]. Administration of a G-CSF antibody neutralizes radiation-induced G-CSF and significantly enhanced mortality in irradiated mice [43]. Interestingly, comparable administrations of the G-CSF antibody to acutely irradiated mice also increase the cell lethality in intestinal tissues (i.e., as reflected by the increased number of apoptotic cells within intestinal villi). In aggregate, these experimental observations clearly indicate that: (a) acute and intense radiation exposures induce markedly elevated levels of circulating G-CSF; (b) the administration of a G-CSF neutralizing antibody exacerbates the deleterious effects of radiation; and (c) G-CSF induction in response to radiation exposure may be playing an important role in recovery.

3. Additive or synergistic effects of combining G-CSF with other drugs

Several agents have been used in combination with G-CSF to enhance its efficacy in various experimental models. However, the possible future use of such therapeutic drug combinations, regardless of effectiveness in treating ARS, may be limited and restricted by the lack of specific EUAs by the US-FDA for such drug combinations. Nevertheless and despite the regulatory hurdles, it seems reasonable to suggest that a number of these drug combinations might prove effective in enhancing the therapeutic potential of recombinant G-CSF in the clinical management of ARS.

A combination of dipyridamole (cellular adenosine uptake inhibitor) and adenosine monophosphate (an adenosine prodrug) exhibited radioprotective efficacy by enhancing hematopoiesis [45]. Combining dipyridamole and adenosine monophosphate enhanced the efficacy of G-CSF [46]. Because the combination of G-CSF, dipyridamole and adenosine monophosphate enhanced endogenous spleen colony formation in irradiated mice, it was interesting to test whether interaction with extracellular adenosine and G-CSF also occurs at the level of the hematopoietic progenitors generating these colonies. Dipyridamole and adenosine monophosphate acted additively with G-CSF to enhance spleen colony formation [47]. These findings indicate that the signaling pathways of G-CSF and drugs elevating extracellular adenosine can interact at the level of multipotential hematopoietic progenitors. Enhancement of the hematopoiesis-stimulating effects of G-CSF by dipyridamole and adenosine monophosphate, which are low-priced and clinically available drugs, may improve the cost-effectiveness of G-CSF therapy.

One study demonstrated that therapeutically administered G-CSF accelerates hematopoietic reconstitution from amifostine-protected stem and progenitor cells, increasing the survival-enhancing effects of amifostine [48]. In this study, female C3H/HeN mice were administered amifostine (200 mg/kg, ip, 30 min before 60Co irradiation) to protect hematopoietic stem cells and G-CSF (125 μg/kg/day, subcutaneously (sc), from day 1 to 16 after irradiation) to stimulate proliferation and reconstitution of the hematopoietic system. This study again reinforces that concept that classic radioprotectors and recombinant hematopoietic growth factors can be used in combination to reduce risks associated with myelosuppression induced by radiation or by radioimetic drugs. The dose reduction factor (DRF) obtained for the amifostine/G-CSF combination-treated mice (1.64) exceeded the DRF of G-CSF-treated mice (1.06) and amifostine-treated mice (1.44). Additionally, bone marrow, splenic multipotential hematopoietic progenitors granulocyte/macrophage-committed progenitors, peripheral white blood cell, platelet, and red blood cell recoveries were accelerated in mice treated with the combination of amifostine and G-CSF. This study was repeated using different doses of the two agents and confirmed their earlier findings [49]. There are several similar reports demonstrating the additive and synergistic effects of G-CSF in combination with synthokine SC-55494 (synthetic IL-3 receptor agonist), glucan (macrophage activator), mast cell growth factor (c-kit ligand), and IL-6 in mouse and NHP models for survival or improvement of myelosuppression (neutropenia/thrombocytopenia) [50–55].

There is an additional report demonstrating the beneficial effects of combining IL-3 and GM-CSF in NHP exposed to 4.5 Gy of mixed fission neutron: γ-radiation [56]. The combined treatment consisted of IL-3 and GM-CSF each administered (sc), two times a day, with doses of 12.5 μg/kg. IL-3 was administered on day 1–7 and GM-CSF on days 7–21. These combined administrations reduced the average 16 days period of neutropenia with antibiotic support in the control animals to 6 days in the treated group. Similarly, the average 10 days period of severe thrombocytopenia, which necessitated transfusions of platelets in the control animals, was reduced to 3 days. There was no improved granulocyte production between the combined administration of IL-3 plus GM-CSF and GM-CSF alone. Also, the combination treatment was less effective than IL-3 alone in reducing thrombocytopenia. Granulocyte function was enhanced in all cytokine-treated animals. We are currently experimenting with a similar combination of amifostine and other radiation countermeasures that induce high levels of G-CSF.

4. Commercially available G-CSF/GM-CSF

Various preparations of G-CSF, pegylated G-CSF, and GM-CSF currently available for clinical use are discussed in the sections below. A summary of these sections has been presented in Table 1.

4.1. Neupogen®

This product is the Amgen Inc. trademark for filgrastim, which has been selected as the name for recombinant methionyl human G-CSF (r-metHug-CSF). As stated above, Neupogen® (Amgen,
Inc.) is a 175 amino acid, 18.8 kDa, protein manufactured by recombinant DNA technology using the E. coli K802 bacteria expression system [57]. Though, the protein has an amino acid sequence that is identical to the natural sequence predicted from the analysis of human DNA, it has an addition of N-terminal methionine, necessary for expression in the analysis of human DNA, it has an addition of N-terminal methionine, necessary for expression in E. coli. Furthermore, it is non-glycosylated also due to being produced by E. coli expression. Thus, Neupogen differs from G-CSF isolated from a human cell (or any mammalian cells).

For cancer patients receiving myelosuppressive chemotherapy, the starting dose of Neupogen is 5 μg/kg/day, administered as a single daily injection by sc bolus injection, short intravenous (iv) infusion (15–30 min) or by continuous sc or iv infusion. Neupogen should be administered daily for up to 2 weeks until the patient’s neutrophil count has reached 10,000/μl following the expected chemotherapy-induced neutrophil nadir. The recommended dose of Neupogen following BMT is 10 μg/kg/day administered iv over a 4 h period starting approximately on day 4 or 11 following the completion of induction chemotherapy. Neupogen is only recommended to patients with known hypersensitivity to E. coli-derived proteins, filgrastim, or any component of the product.

4.2. Tevagrasitmin/Tbo-filgrasitmin

As stated above, Tbo-filgrastim (Sicor Biotech UAB, distributed by: Teva Pharmaceuticals USA, North Wales, PA) is another form of G-CSF, developed following the expiration of the Neupogen patent. Tbo-filgrastim was approved, with narrower indications than those for Neupogen, to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs that are associated with a clinically significant incidence of febrile neutropenia. The recommended dose of Tbo-filgrastim is 5 μg/kg/day administered as a sc injection. Daily dosing with Tbo-filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range [16].

4.3. Neulasta

Neulasta (PEGfilgrastim; Amgen, Inc.) is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia [17,18]. Unlike Neupogen, Neulasta is not indicated for mobilizing peripheral blood progenitor cells for hematopoietic stem cell transplantation. The recommended dosage of Neulasta is a single sc injection of 6 mg administered once per chemotherapy cycle.

4.4. Leukine/Sargramostim

Leukine (Sanofi-Aventis U.S. LLC, Bridgewater, NJ, USA) is a recombinant human GM-CSF (rhGM-CSF) produced by recombinant DNA technology using the Saccharomyces cerevisiae (yeast) expression system. Leukine is a glycoprotein consisting of 127 amino acids, characterized by three primary molecular species, having molecular weights of 19,500, 16,800 and 15,500 Da. The amino acid sequence of Leukine differs from the natural human GM-CSF by a substitution of leucine at position 23, and the carbohydrate moiety may be different from the native protein. Sargramostim was selected as the proper name for yeast-derived rhGM-CSF.

For neutrophil recovery following chemotherapy for acute myelogenous leukemia, the recommended dose of Leukine is 250 μg/m^2/day administered iv over a 4 h period starting approximately on day 4 or 11 following the completion of induction chemotherapy. The recommended dose for post-peripheral blood progenitor cell transplantation is 250 μg/m^2/day administered iv over a 2-h period beginning 2–4 h after bone marrow infusion, and no less than 24 h after the last dose of chemotherapy or radiotherapy (details obtained from product sheet) [58].

5. Stockpile of G-CSF to treat ARS

The Centers for Disease Control’s Strategic National Stockpile (SNS) is a national repository of antibiotics, chemical antidotes, antitoxins, life-support medications, iv administration items, airway maintenance supplies, and medical/surgical items. The SNS is designed to supplement and re-supply state and local public health agencies in the event of a national emergency anywhere and anytime within the US or its territories [59]. The US Department of Health and Human Services (HHS) will transfer authority for the SNS material to the state and local authorities once it arrives at the designated receiving and storage site. The SNS is
organized for a flexible response. The first line of support lies within the immediate response 12-h Push Packages. These are caches of pharmaceuticals, antidotes, and medical supplies designed to provide rapid delivery of a broad spectrum of agents for an ill-defined threat in the early hours of an event. These Push Packages are positioned in strategically located, secure warehouses ready for immediate deployment to a designated site within 12 h of the federal decision to deploy SNS assets. The SNS program ensures that the medical material stock is rotated and kept within potency shelf-life limits [22,60,61].

The HHS Office of the Assistant Secretary for Preparedness and Response Biomedical Advanced Research and Development Authority, Project BioShield is the chief mechanism through which the US government supports the advanced development and procurement of new medical countermeasures—drugs, vaccines, diagnostics, and medical supplies—to protect the health of US citizens against chemical, biological, radiological and nuclear threats. Under the Project BioShield Act of 2004, the Biomedical Advanced Research and Development Authority has supported the development and procurement of medical countermeasures, drugs and products to treat illnesses ranging from anthrax, smallpox, and botulism to the impacts of ionizing radiation.

As previously stated, G-CSF and GM-CSF are approved by the US FDA for cancer patients undergoing chemotherapy to speed white blood cell recovery and reduce the risk of infection. In 2013, HHS awarded a $157.5 million contract to Amgen USA Inc., to purchase Neupogen® (Filgrastim: G-CSF) [62]. The leukocyte growth factors acquired under this contract will remain in the possession of the manufacturers in vendor-managed inventory until they are needed. The companies will rotate this inventory to meet commercial demand so the inventory does not expire. This was the first time under Project BioShield that commercially available products were purchased to establish a sustainable emergency response capability. HHS also awarded a $36.5 million contract to Sanofi-Aventis for late-stage development and procurement of Leukine® (Sargramostim: GM-CSF).

Although G-CSF has not been approved by the FDA for treating ARS victims, it has been procured (along with GM-CSF) to be stockpiled in the SNS under the Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA) of 2013. PAHPRA significantly expands FDA authority to support medical countermeasure preparedness and response efforts for chemical, biological, radiological, or nuclear (CBRN) emergencies [63]. PAHPRA clarifies part of the FDA’s authority to issue EUA, which allows use of unapproved medical products or unapproved uses of approved products leading up to or during an emergency in the absence of adequate, approved, and available alternatives. There are instances when the FDA issues EUAs ahead of a declared emergency; these instances include when HHS determines that there is significant potential for an emergency involving a CBRN agent that affects or has significant potential to affect national security or the health and security of US citizens abroad. Governmental pre-prepositioning permits federal, state, and local governments to pre-position medical countermeasures in anticipation of approval or clearance, or issuance of a EUA to enable them to better prepare for potential rapid deployment during an actual CBRN emergency.

6. Preclinical efficacy of G-CSF and GM-CSF across various species

Preclinical studies in mouse, canine, mini-pig, and NHP models demonstrate reduced severity of myelosuppression with enhanced neutrophil recovery and improved survival after G-CSF or GM-CSF treatments when exposed to lethal or sub-lethal doses of radiation (Table 2). We focus our discussion below on the effects on survival and on the recovery of blood leukocytes (neutrophils) conducted in different animal models. In a majority of studies, survival and blood response profiles were primary efficacy endpoints. We have divided this section into G-CSF and GM-CSF to better organize all studies conducted with these CSFs.

6.1. Studies with G-CSF

The radioprotective efficacy of G-CSF has been evaluated in different strains of mice, canines (beagle), and NHP, with one recent report of using G-CSF therapeutically in the minipig [64]. A majority of these studies have used recombinant G-CSF of human origin because G-CSF is not species-specific. Most of the investigators have used Amgen’s recombinant G-CSF (Neupogen®/filgrastim) but a few have used G-CSF from other sources. The results of multiple studies suggest that G-CSF consistently enhanced survival and the recovery of blood leukocytes (neutrophils) across various species (mice, beagle, minipig, and NHP) regardless of radiation source (γ-ray, X-ray, mixed field—neutron and gamma). The demonstrated radioprotective efficacy of G-CSF was dependent on drug dose, the drug treatment schedule in relation to radiation exposure, duration of the treatment and the dose of radiation. The estimated DRFs for G-CSF were 1.06 [48], 1.1 [65] or 1.2 [66], depending on G-CSF dose, treatment schedule, route of administration, and strains of mice [67]. The rhG-CSF increased the number of blood-circulating neutrophils, monocytes and erythrocytes, but not that of lymphocytes and thrombocytes.

Various treatment schedules were reported as well: for example, rhG-CSF administered twice (1 μg/dose, twice daily, ip, day 0–6) protected BDF1 mice against 8.5 Gy X-ray (0.6 Gy/min) TBI [68]. Another study reported that rhG-CSF (100 μg/kg/day, sc starting 1 h after radiation exposure for the next 3 days (Neutrogenin®, Choongwae, Seoul, Korea) protected C3H/HeN mice against partial-body irradiation (12 Gy, 3.8 Gy/min, abdominal exposure) [69], G-CSF also protected C3H/HeN female mice when administered 2.5 μg/day, sc, on days 3–12 following 8 Gy total body irradiation (TBI) [53]. In a mouse survival assay, G-CSF (0.34 mg/kg, sc, 12, 24, and 48 h after irradiation) also was effective as a post-irradiation mitigator against injuries stemming from both γ-photons (8.0–9.0 Gy and mixed-field irradiation (8.0, 8.5 and 9.0 Gy γ-rays and 4.63, 4.92, and 5.21 Gy mixed field, respectively) [70]. In a recent study it has been observed that G-CSF appears to protect both irradiated and combined injury (irradiated and wounded) mice. G-CSF has not been tested in a murine combined injury model of irradiation and burn [71].

Contrary to the above positive findings of therapeutic effectiveness of these recombinants, there is one report in a mouse model where the use of G-CSF did not show a survival benefit [72]. This study administered a single ip dose of G-CSF (up to 2 μg/mouse) one or 3 h after 8 Gy (LD95/30) 60Co TBI. This study did show however that recombinant GM-CSF also failed to show efficacy but recombinant human IL-1, recombinant murine interferon-γ, and recombinant human tumor necrosis factor were effective. In addition, reports suggest variable responses of G-CSF in different strains of mice, and the optimal dose of G-CSF also varies in different strains [73,74]. In these studies, however, G-CSF was administered very shortly following irradiation and not therapeutically to irradiated animals.

The estimated DRFs for acutely irradiated canines (beagles) given therapeutic doses of recombinant G-CSF (10 μg/kg/day, sc, daily for 21 days starting on day 1 post-TBI) and with or without full supportive care were 1.73 and 1.34, respectively [75]. The supportive care regimen consisted of infusions of fluids, antibiotics, and fresh irradiated platelets. In another study, eight out of ten canines receiving G-CSF (Amgen; 10 μg/kg/day, sc, twice a day for 21 day) survived with complete and sustained hematopoietic
G-CSF/filgrastim/Neupogen\(^\text{a}\)  
Mice  
125 µg/kg/day, sc, day 1–16 post-irradiation  
2.25 µg/mouse, ip, twice a day, days 1–14 post-irradiation  
1 mg/kg, 2 h after irradiation  
Various doses and schedules in different strains of mice  
0.34 mg/kg, sc, 12, 24, and 48 h post-irradiation, (8.0, 8.5 and 9.0 Gy γ-rays, 4.63, 4.92, and 5.21 Gy neutron for mixed field, respectively)  
2 µg/mouse, ip, 1 or 3 h after 6 Gy (LD\(_{50/60}\)) \(^\text{b}\) \(^\text{c}\) of single or multiple doses.  
Treatment enhanced survival and stimulated hematopoietic recovery or improving survival after severe, radiation-induced myelosuppression  
Treatment was not effective in promoting hematopoietic recovery or improving survival  
No radiomitigative efficacy observed  
Treatment protected C3H/HeN mice against partial-body irradiation  
Treatment demonstrated efficacy of G-CSF when administered before radiation exposure  
Treatment improved survival, leukopenia, and neutropenia compared to control  
References  

Studies conducted with G-CSF or GM-CSF in combination with other cytokines in various animal models have not been included in above table.

Fission-neutron radiation damage is generally difficult to treat due to the combined nature and repair of injuries to both the hematopoietic and GI systems. However, in at least one study, the therapeutic effect of rhG-CSF (Hangzhou Jiuyuan Gene Engineering Co., Hangzhou, China) was clearly demonstrated. In this study, dogs received 2.3 Gy, whole-body, mixed fission-neutron-gamma irradiation with a high ratio of neutrons (~50%) \(^\text{[80]}\). Following irradiation, rhG-CSF treatments were administered (10 µg/kg/day, sc, once a day starting within 1 h of irradiation and continued for 21 days), resulting in 100% survival of the treated group vs 60% survival in control group. Only two of five rhG-CSF-treated dogs experienced leukopenia (white blood cell, WBC < 1.0 × 10\(^9\)/L) and neutropenia (neutrophil < 0.5 × 10\(^9\)/L), whereas all irradiated controls displayed a profound period of leukopenia and neutropenia. Furthermore, administration of rhG-CSF significantly delayed the onset of leukopenia and reduced the duration of leukopenia as compared with controls. Thus, these results demonstrated that rhG-CSF administration enhanced recovery of myelopoiesis and survival after fission neutron-irradiation.

Clinically beneficial effects of recombinant G-CSF treatments have been reported recently for acutely gamma irradiated (LD\(_{50/30}\) TBI, 1.78 Gy) minipigs (male Gottingen minipigs, 4–5 months of age). A post-exposure treatment regimen consisting of rhG-CSF at 10 µg/kg/day, sc, starting 24 h after TBI, resulted in enhanced survival and stimulated recovery from neutropenia \(^\text{[64]}\). However, additional studies will be needed to judge the suitability of this animal model for studying radiation countermeasures.

An extended, carefully conducted study in NHPs (Macaca mulatta, Chinese substrain) of rhG-CSF’s (filgrastim) efficacy has clearly demonstrated a survival benefit associated with such treatments. In this study, a cohort of 46 randomized animals, 24 filgrastim-treated (20 male and 4 female) and 22 control (18 male and 4 female) \(^\text{[82]}\) was exposed to an LD\(_{50/30}\) dose (7.5 Gy, an approximate mid-lethal dose, 0.8 Gy/min) of 6 MV linear accelerator-derived photon radiation. Filgrastim (10 µg/kg/day, sc) was administered, beginning 1 day after irradiation and continued until day 21. The treatment enhanced survival and stimulated hematopoietic recovery in the C57BL/6 male/mouse strain, while no radiomitigative efficacy was observed in the C3H/HeN mice. The treatment protected the C3H/HeN mice against partial-body irradiation and improved survival, leukopenia, and hematopoietic recovery after severe, radiation-induced myelosuppression. The treatment was not effective in promoting hematopoietic recovery or improving survival, but significantly delayed the onset of leukopenia and reduced the duration of leukopenia as compared with controls. Thus, these results demonstrated that rhG-CSF administration enhanced recovery of myelopoiesis and survival after fission neutron-irradiation.
daily until the absolute neutrophil count was >1,000/µl for 3 consecutive days. All NHPs received medical management/supportive care [81]. Overall, the primary end point was survival at 60 days post-irradiation. Secondary end points included mean survival time of decedents and other hematologic parameters. Again, as indicated earlier, filgrastim effectively mitigated the lethality stemming from the hematopoietic component of ARS. Specifically, filgrastim significantly reduced 60 day overall mortality (20.8% (5/24)) compared to controls (59.1% (13/22)). Filgrastim also decreased the duration of neutropenia but did not affect the absolute neutrophil count nadir. Survival significantly increased compared to controls.

G-CSF generally enhanced hematopoietic recovery in all animal species and strains studied [48, 51, 64, 67, 68, 76–80, 82–87]. The beneficial effects of G-CSF were measured as decreased duration of neutropenia, decreased time for neutrophil recovery, improved neutrophil nadir, increased WBC count, and increased granulocyte/macrophage colony-forming units (GM-CFU) in bone marrow. As a consequence of such observations that support the concept that recombinant G-CSF treatments provide substantial therapeutic benefit, the Centers for Disease Control and Prevention currently has an IND Application (with the US FDA) containing a detail clinical protocol for how G-CSF/filgrastim would be administered to exposed victims in the event of a radiological nuclear incident [23].

6.2. Studies with pegylated G-CSF

Modification of proteins with polyethylene glycol (PEG) results in increased size which reduces renal clearance and prolongs half-life, thereby reducing the need for daily dosing. One such amended recombinant growth factor, Neulasta® (pegylated human G-CSF, Amgen, Inc.), has demonstrated efficacy of neutrophil recovery enhancement in animals and humans with drug- or radiation-induced neutropenia, utilizing only one or two doses. The pegylated G-CSF molecule has more potent hematopoietic properties than corresponding non-pegylated G-CSF [88]. Neulasta® (as well as Maxy-G34) has been bioengineered to contain 5 amino acid substitutions of the native G-CSF and three polyethylene glycol conjugations at unique site and has been demonstrated protective efficacy in C57BL/6 male/female mice against 8.7 Gy (137Cs) when administered as a single sc dose (100 µg/kg) at 24 ± 4 h post-TBI [89]. The ‘one low dose administration’ schedule is an attractive attribute of the survival rate was similar between the recombinant canine GM-CSF-treated group (1/10) and an untreated group (1/13) in a canine model with supportive care (parenteral fluids, electrolytes, platelet transfusions, and antibiotics) [76]. In this study, canines received 4 Gy 60Co TBI and within 2 h of TBI, GM-CSF was administered sc at a dose of 50 µg/kg twice a day for 5 doses and then continued at 25 µg/kg twice daily for 21 days or until death. Nine canines died between days 11–21. The causes of death were reported as pneumonia (n = 7) or sepsis (n = 2). GM-CSF was not effective in promoting hematopoietic recovery or improving survival. The lack of efficacy was not due to GM-CSF itself because GM-CSF (50 µg/kg/day for 14 days, sc) increased neutrophil counts (3.0–9.3 times the baseline) in five non-irradiated canines. In the same study, recombinant canine G-CSF enhanced survival.

The ability of rhGM-CSF to enhance recovery of a radiation-suppressed hematopoietic system was evaluated in a partial-body radiation exposure model using rhesus NHPs [92]. rhGM-CSF treatment for 7 days after a lethal, non-uniform radiation exposure of 8 Gy was sufficient to enhance hematopoietic reconstitution, leading to an earlier recovery. rhGM-CSF (6.25 × 10^8 U/mg, from Genetics Institute, Inc., Cambridge, MA) was administered iv as a single dose of 50,000 U on either days 3 or 4 following irradiation followed by subsequently continuous sc administration via an implanted pump with 72,000 U/kg/day of the recombinant for 7 additional days. The two treatments partially restored circulating blood levels of granulocytes and platelets levels, 4 and 7 days earlier than control NHPs, respectively. GM-CFU activity in the bone marrow was monitored to evaluate the effect of rhGM-CSF on recovery of myeloid elements within bone marrow. Noting that treatment with rhGM-CSF led to an early recovery of GM-CFU activity, the authors suggested that rhGM-CSF might be acting on an earlier stem cell population to generate GM-CFU.

In a majority of studies conducted in different animal models, GM-CSF enhanced blood leukocyte recovery in various strains of mice [52, 73, 83, 91], beagle canines [75, 93, 94], and rhesus NHPs [56, 82, 95] when administered alone or in combination with other cytokines. As stated for G-CSF, the effects were assessed mainly as...
decreased duration of neutropenia, decreased time for neutrophil recovery, improved neutrophil nadir, increased WBC counts, and increased GM-CFU in bone marrow.

Variations in preparation and sources of GM-CSF as well as difference in study design may contribute to the inconsistent survival benefits of GM-CSF. Results available in the published literature support using GM-CSF to enhance blood leukocyte recovery during the hematopoietic phase of ARS, however, the published results of the survival benefit are less convincing. There are studies where the efficacies of G-CSF and GM-CSF have been compared in concurrent experiments in mice and canines, specifically in terms of a survival benefit: results of these comparative studies have shown that G-CSF was found to be more effective in protecting irradiated animals compared with GM-CSF [73,76].

7. G-CSF/GM-CSF used for the treatment of radiological/nuclear accident victims

Radioactive materials continue to be used in a variety of industries, including but not limited to energy production, construction, medicine, and research. Concerns over adverse effects of nuclear/radiological exposures of industrials workers and the general population continue. Exposure safeguards are clearly essential in order to protect people from the detrimental effects of undue levels of ionizing radiation. Where the quantity of radioactive material is substantial, e.g. with sources used in radiotherapy or industrial radiography, extreme care is necessary to prevent accidents that may have severe consequences for the individuals affected. In spite of all precautions, accidents with radiation sources continue to occur, although infrequently.

Approved indications of CSF that are potentially relevant in the treatment of ARS include use in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy or with subsequent BMT. Use of G-CSF and GM-CSF is based on the established biologic mechanism of G-CSF/GM-CSF, which stimulate neutrophil production, accelerate neutrophil recovery, and reduce the severity and duration of febrile neutropenia and infections.

Although CSFs have been used with several accident victims (Table 3), there is no randomized trial for the effectiveness of the recombinant CSFs in patients exposed to high doses of ionizing radiation; further, in such cases in which recombinant CSF has been used therapeutically, the specific CSF product was not always identified. Additional limitations of these case studies include the variable radiation doses, use of growth factors other than G-CSF/GM-CSF, large variability in the CSF dose, time of CSF administration in relation to radiation exposure, and duration of CSF administration. The consensus guidelines recommend starting CSF as soon as possible [22,96,97]. In some cases, CSF administration was not initiated until weeks after the incidence [58].

There have been a larger number of accidents involving sealed radioactive sources, such as $^{60}$Co, $^{192}$Ir, or $^{137}$Cs than accidents involving nuclear power plants, accidents in the radiation therapy of patients, or accidents in other radiation industries [23,98]. Radiation accident reports show that CSFs have been used in a wide variety of accident situations [99,100]. Although the first CSF was approved by the US FDA in 1991, the first known use of CSF was for the Chernobyl, nuclear power plant accident in Ukraine in 1986. A year later, CSFs were used in Goiânia, Brazil, for a radiological exposure accident involving an abandoned radiation source. Here, we briefly describe all radiation incidents since 1986, for which CSF was used to treat the radiation exposed victims. Although the data seem to indicate that the period of neutropenia is shortened and survival prolonged, there is no definitive proof that CSF administration actually decreases mortality in radiation-exposed humans. CSF therapy is considered a valuable adjunct to treatment with antibiotics and strict hygiene controls in radiation-exposed victims.

7.1. Chernobyl disaster, Soviet Union/Russia 1986

The Chernobyl disaster was a catastrophic nuclear accident that occurred on 26 April 1986 at the Chernobyl Nuclear Power Plant in Ukraine (then the Ukrainian SSR), which was under the Soviet Union [101,102]. An explosion and fire released large quantities of radioactive particles into the atmosphere, which spread over much of the western USSR and Europe. The Chernobyl disaster is widely considered to have been the worst nuclear power plant accident in history, and is one of only two Level 7 classified events on the international nuclear event scale (the other being the Fukushima Daiichi nuclear disaster of 2011).

Of 600 workers present on the site of the accident, 134 received high doses (0.8–16 Gy) and suffered from radiation sickness. Out of 134 victims, 28 died within 3 months, and another 19 died between 1987 and 2004 of various causes not necessarily associated with radiation exposure. In addition, the majority of the 530,000 registered recovery operation workers received doses between 0.02 Gy and 0.5 Gy between 1986 and 1990 [101]. In April 2013, previously classified data regarding the Chernobyl accident were released, demonstrating that three accident victims, with an estimated exposure dose of 5 Gy, were administered GM-CSF, (Sandoz Pharma Ltd., Basel, Switzerland) six weeks after the accident. Following radiation exposures, but prior to treatments with recombinant drug, the patients exhibited severe granulocytopenia, with life threatening lung diseases from radiation pneumonitis as well as infection(s) that were unresponsive to antibiotics, anti-fungal and anti-viral agents. Since no previous use of GM-CSF in humans had been demonstrated at that time, the authors (Dr. A. Vorobiov and R.P. Gale of the USSR) injected themselves with GM-CSF before administering it to the patients. AV had no immediate side effects but reported severe, transient pain in the sacrum, which required iv morphine [102,103]. RPC’s injection was without any complication. Bone marrow pain is now a well-known side effect of G-CSF and GM-CSF administrations. Out of the three victims treated with GM-CSF (treatment schedule not available), one died of progressive pneumonia (respiratory failure) 2 days after administration, the other two had hematopoietic recovery and survived [103]. The authors (recipients of GM-CSF) have not experienced adverse effects after twenty-seven years of GM-CSF administration.

7.2. Radiotherapy source accident, Goiânia, Brazil, 1987

The Goiânia accident occurred on 13 September 1987 in the Brazilian state of Goiás [104,105], after an old radiotherapy source ($^{137}$Cs) was stolen from an abandoned hospital site in the city. The radioactive source was in the form of cesium chloride salt, which is highly soluble and readily dispersible. Contaminations of the environment lead to external radiation exposure and also internal contamination of several individuals. After the source capsule ruptured, the remnants of the source assembly were sold for scrap. One buyer noticed that the source material glowed blue in the dark making it attractive. Several persons were fascinated by this and over a period of days friends and relatives came and saw the phenomenon. Fragments of the source (the size of rice grains) were distributed to several families. This went on for 5 days and a number of people began showing GI symptoms arising from their exposure to radiation from the source. The symptoms were not initially recognized as being due to radiation exposure. However, one of the exposed persons took the remnants to the public health department in the city. This action began a chain of events which led to the discovery
of the accident. About 112,800 people were examined for radioactive contamination, 249 individuals required medical treatment, 20 victims were hospitalized, and of these, 8 had severe bone marrow impairment. Of the internal contamination victims, 46 were treated with Radiogardase (Prussian Blue or ferric ferrocyanide)\[104\].

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The International Atomic Energy Agency (IAEA) called it "one of the world's worst radiological incidents". The operator bypassed the safety systems and entered the radiation exposure room with two other workers to free the source rack. The movable source rack became stuck in the irradiation position. The operator bypassed the safety systems and entered the radiation exposure room with two other workers to free the source rack. The movable source rack became stuck in the irradiation position.


A radiological accident occurred on 5th February 1989 at San Salvador \[106,107\], El Salvador. A radioactive $^{60}$Co source in a movable source rack became stuck in the irradiation position. The operator bypassed the safety systems and entered the radiation exposure room with two other workers to free the source rack manually. The three individuals received high radiation doses and developed ARS. Their initial hospital treatment in San Salvador and subsequent, more specialized treatment in Mexico City, were partially effective in countering the acute effects.

Their estimated exposure doses were 3.0–8.1 Gy. On days 24, 26, and 32 after exposure, each victim received rhGM-CSF were initiated, succumbed to their injuries. This clinical case study highlighted several important points: first, the rapid rise in granulocytes within 12 h of GM-CSF administration; second, the decline in granulocytes after drug dose attenuation or discontinuation; and third, the apparent different patterns of recovery in treated and untreated victims \[105\].

It should be noted that published information reporting treatment of Delhi, India accident victims was later retracted by the authors. Limited details are available for all accidents (additional details for various victims are not available).

<table>
<thead>
<tr>
<th>Year</th>
<th>Place</th>
<th>Radiation source</th>
<th>Exposure</th>
<th>Treatment details and outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>Chernobyl, Ukraine</td>
<td>$^{40}$Co radionuclides</td>
<td>Acute</td>
<td>GM-CSF treatment details not available, two exposed victims recovered and one died</td>
<td>[102,103]</td>
</tr>
<tr>
<td>1987</td>
<td>Goiânia, Brazil</td>
<td>$^{137}$Cs</td>
<td>Protracted</td>
<td>Four victims who received GM-CSF (300 $\mu$g/m$^2$/day, iv, dose reduced to half when neutropenia improved) 5 days before developing neutropenia and infection survived, other four with infection at the time of GM-CSF initiation died</td>
<td>[104,105]</td>
</tr>
<tr>
<td>1989</td>
<td>San Salvador, El Salvador</td>
<td>$^{60}$Co</td>
<td>Acute</td>
<td>GM-CSF (240 $\mu$g/m$^2$/day, iv), neutrophil counts improved after 9 or 10 days after treatment initiation, victim with highest dose of exposure (~8 Gy) died, other two with 2.92 and 3.77 Gy exposure doses survived</td>
<td>[106,107]</td>
</tr>
<tr>
<td>1990</td>
<td>Soreq, Israel</td>
<td>$^{60}$Co</td>
<td>Acute</td>
<td>GM-CSF (250 $\mu$g/m$^2$/day) from day 1 to 18, also IL-3 from day 5–18, blood cell count improved, given BMT and died on day 36 due to graft vs host disease</td>
<td>[108]</td>
</tr>
<tr>
<td>1992</td>
<td>Nesvizh, Belarus</td>
<td>$^{60}$Co</td>
<td>Acute</td>
<td>GM-CSF (11.4 $\mu$g/kg/day, 1–6 days, 6 $\mu$g/kg/day, 16–39 days) and IL-3 (10 $\mu$g/kg/day, day 6–31), marrow and blood cell recovered, victim died on day 108 due to pneumonia and acute respiratory failure</td>
<td>[109]</td>
</tr>
<tr>
<td>1996</td>
<td>Gilan, Iran</td>
<td>$^{131}$I</td>
<td>Acute</td>
<td>Five victims: 2.2–3.1 Gy, GM-CSF (8 $\mu$g/kg/day for 11/12 days), Two victims: 0.8–2 Gy, G-CSF (5 $\mu$g/kg/day for 11/12 days), Neutrophil and lymphocytes recovered and all survived</td>
<td>[110]</td>
</tr>
<tr>
<td>1998</td>
<td>Istanbul, Turkey</td>
<td>$^{60}$Co</td>
<td>Acute</td>
<td>GM-CSF (400 $\mu$g/m$^2$/day twice daily, sc, day 22–24, then 300 $\mu$g/m$^2$/day twice daily for 10 days), BMT on day 24, recovered</td>
<td>[111]</td>
</tr>
<tr>
<td>1999</td>
<td>Henan Province, China</td>
<td>$^{60}$Co</td>
<td>Protracted</td>
<td>GM-CSF (11.4 $\mu$g/kg/day, 1–6 days, 6 $\mu$g/kg/day, 16–39 days) and IL-3 (10 $\mu$g/kg/day, day 6–31), marrow and blood cell recovered, victim died on day 108 due to pneumonia and acute respiratory failure</td>
<td>[104,111-113]</td>
</tr>
<tr>
<td>1999</td>
<td>Tokai, Japan</td>
<td>Gamma (γ) + Neutron (n)</td>
<td>Protracted</td>
<td>GM-CSF (100 $\mu$g/kg/day), EPO, TPO as needed, received peripheral blood stem cell transplant, died on day 82. B. 4.5 Gy γ, 2.9 Gy n, G-CSF (5 $\mu$g/kg/day for 11/12 days), Neutrophil and lymphocytes recovered and all survived</td>
<td>[114-116]</td>
</tr>
<tr>
<td>1999</td>
<td>Yanango, Peru</td>
<td>$^{131}$I</td>
<td>Protracted</td>
<td>GM-CSF (300 $\mu$g/kg/day, day 35–42, victim survived</td>
<td>[104,117-118]</td>
</tr>
<tr>
<td>2000</td>
<td>Prakan, Thailand</td>
<td>$^{60}$Co</td>
<td>Protracted</td>
<td>GM-CSF (5–10 $\mu$g/kg/day and increased to 20 $\mu$g/kg/day) and GM-CSF (300 $\mu$g/kg/day and increased to 300 or 600 $\mu$g/kg/day), six survived, three died on days 38, 47, and 53</td>
<td>[119,120]</td>
</tr>
<tr>
<td>2000</td>
<td>Meet Hala, Egypt</td>
<td>$^{131}$I</td>
<td>Protracted</td>
<td>GM-CSF (10 $\mu$g/kg/day), all five survived</td>
<td>[121,122]</td>
</tr>
<tr>
<td>2005</td>
<td>Nueva, Aldea, Chile</td>
<td>$^{131}$I</td>
<td>Acute</td>
<td>GM-CSF (10 $\mu$g/kg/day, day 6–8 post-radiation exposure), victim survived</td>
<td>[123]</td>
</tr>
<tr>
<td>2006</td>
<td>Fleurus, Belgium</td>
<td>$^{60}$Co</td>
<td>Acute</td>
<td>Pegylated G-CSF (6 mg/d, initiated on day 28), pegylated EPO and stem cell factor (on days 32 and 33), victim recovered</td>
<td>[100]</td>
</tr>
<tr>
<td>2006</td>
<td>Dakar, Senegal</td>
<td>$^{131}$I</td>
<td>Protracted</td>
<td>Pegylated G-CSF (6 mg/d, recombinant SCF (Stemgen), and pegylated EPO, victim recovered</td>
<td>[100]</td>
</tr>
<tr>
<td>2010</td>
<td>Delhi, India</td>
<td>$^{60}$Co</td>
<td>Protracted</td>
<td>GM-CSF (5 $\mu$g/kg), one with 3.1 Gy exposure died on day 46, other two survived</td>
<td>[124–127]</td>
</tr>
</tbody>
</table>
A 60Co teletherapy source was sold as scrap metal in 1999. The dose estimates for the second and third victims were 3.77 and 2.92 Gy, respectively. Both of these victims survived following GM-CSF treatment.

7.4. Irradiator operator accident, Soreq, Israel, 1990

A fatal radiological accident occurred on 21 June 1990 [106,108], at an industrial facility at Soreq, Israel. An operator entered into the whole-body irradiation room and was exposed to an estimated whole-body dose of 10–20 Gy (60Co) [108]. The accident happened after the irradiation source rack became stuck in the irradiation position owing to obstruction by cartons on the internal conveyor. The operator, having misinterpreted two conflicting warning signals, bypassed installed safety procedures in order to enter the irradiation room to free the blockage. After a minute or so in the irradiation room, the operator felt a burning sensation in his eyes and pounding in his head. He left the room and reported the incident to a superior. Shortly afterwards he felt sick and started to retch. He was immediately taken to a hospital where immediate care was provided. He presented signs and symptoms indicative of severe hematological and GIS of ARS. Localized skin injury due to radiation exposure also developed.

The rhGM-CSF treatment was started approximately 9 h after exposure as a continuous infusion and continued for 18 days at a dose of 250 μg/m²/day. A BMT was performed on day 4 after exposure. The victim was treated with IL-3 on days 5–18. Growth factors were discontinued on day 18 due to normalization of white blood cell counts. The victim died on day 36, probably from graft vs host disease. Data were thought to indicate that a combination of rhGM-CSF and IL-3 may lead to early and effective engraftment and maturation of donor marrow cells [106]. This was the first case in which rhGM-CSF was administered early (about 9 h after radiation exposure).

7.5. Sterilization facility accident, Nesvizh, Belarus, 1992

On 26 October 1991 [109], one victim received an estimated whole-body exposure of about 11 Gy (with localized area of up to 20 Gy) from a 60Co source at an industrial sterilization facility. This victim received GM-CSF (day 1–6 (11.4 μg/kg/day) and day 16–39 (6 μg/kg/day), and IL-3 (day 6–31; 10 μg/kg/day). Neutrophil recovery started on day 21, and reticulocytes appeared 10–12 days later. No platelet recovery occurred. Granulocytes reached a level of 5 × 10⁹/L on day 40. The patient died on day 108 from pneumonia and acute respiratory failure. Hematopoietic recovery was incomplete but results suggest improvement due to the growth factor therapy [109].

7.6. The radiological accident, Gilan, Iran 1996

On 24 July 1996 [110], an accident occurred at the Gilan combined-cycle fossil fuel power plant in the Islamic Republic of Iran. A worker put an unshielded 185 Gbq 192Ir source in his pocket for few h, unaware that the object was an unshielded source used for industrial radiography [110]. Cytogenetic dosimetry indicated a whole-body estimated dose exposure of about 4.5 Gy. He was treated with prophylactic antibiotics and transfused with 7 units of platelets on day 20 after exposure. Transfusion of platelets on day 20 produced a transient rise in platelet count, but by day 22 it was clear that further therapy was required, so G-CSF (Leumomax, Schering Plough, Kenilworth, NJ, now known as Merck) treatment was initiated (400 μg/m² twice daily, sc) [110]. The victim was transferred to Paris for possible BMT on day 24. There, platelet transfusions and antibiotics were continued. G-CSF therapy was continued at a dose of 300 μg/m²/day for 10 more days until the white blood cell count showed marked improvement. A marrow sample taken from the right iliac crest on day 35 showed marrow with essentially normal appearance, with all cellular elements present and without abnormal forms. This finding was surprising as the previous marrow sample, taken on day 20 from the opposite iliac crest, was acellular. A skin graft for the chest lesion was performed on day 63. By 15 October 1996 (day 84) he appeared to have recovered completely, and he was therefore transferred back to his physician in Tehran on day 95. The intervention with cytokines probably made only a small contribution to the eventual recovery because treatment was initiated at a stage where bone marrow recovery was already under way. However, the use of G-CSF may have accelerated the recovery process.

7.7. Teletherapy source accident, Istanbul, Turkey, 1998

A 60Co teletherapy source was sold as scrap metal in 1999. The persons who purchased these packages broke open the shielded containers, exposing them and several others to radiation in December 1998 and again in January 1999. Eventually a total of 10 adults showed signs and symptoms of acute radiation exposure. About 4 weeks after exposure, filgrastim treatment was initiated to the seven most severely affected victims and continued on G-CSF for 6–12 days [111]. The estimated radiation exposure doses based on dicentric analysis for the 7 most heavily exposed individuals ranged from 0.9–3.1 Gy; five of the worst victims were estimated to have exposures between 2.2 and 3.1 Gy. G-CSF therapy (8 μg/kg/day) was discontinued after 6 days for patients 5–7 (5 μg/kg/day), who were in a less severe condition (exposure dose 0.9–2 Gy), and after 11–12 days of initiation for patients 1–4, who were in more severe condition.

Five patients with life-threatening thrombocytopenia received platelet and whole blood transfusions. All victims treated with G-CSF survived. The five most severely affected victims left hospital after 45 days. Although five victims recovered rapidly after massive platelet transfusions (24 units), all other patients showed marked recovery in platelet counts after completion of G-CSF treatment. Such platelet recovery delay has been reported previously, and this appears to be a negative attribute of G-CSF treatment.

7.8. Cobalt source accident, Henan Province, China, 1999

In April 1999 [112], a 60Co source was sold as scrap metal in China’s Hunan province. The dealer who purchased it, brought the source to his home, exposing himself, his wife and 8-year-old son with estimated doses of 2.4, 6.1, and 3.4 Gy, respectively. All three received GM-CSF treatment when their total white cell count was below 1 × 10⁹/L. The scrap metal dealer received 400 μg/m²/day GM-CSF from day 26–35 and 120 U/kg/day EPO from day 10 to 36. His wife received 400 μg/m²/day GM-CSF from day 9 onward until day 33 when it was decreased to 200 μg/m²/day and stopped on day 37. She received testosterone for 7 days to delay menstruation and blood loss, and like her husband, received EPO when her hemoglobin was <90 g/L. His son received 200 μg/m²/day GM-CSF starting on day 18 until day 33 when it was decreased to 50 μg/m²/day, and stopped on day 36 [112]. Gamma globulin, whole blood, and fresh platelets were provided to each patient. All patients recovered by day 83 of treatment.
7.9. Criticality accident, Tokaimura, Japan, 1999

The Tokaimura nuclear accident occurred on September 30 [113–116], 1999, resulting in two deaths. It was the worst civilian nuclear radiation accident in Japan prior to the Fukushima Daiichi nuclear disaster of 2011. The criticality accident occurred in a uranium reprocessing facility when three workers were preparing a small batch of fuel for an experimental fast breeder reactor, using uranium enriched to 18.8%. The precipitation tank reached critical mass when its fill level, containing about 16 kg of uranium, reached about 40 L. The tank was not designed to hold this type of solution and was not configured to prevent criticality [113].

There were 56 plant workers whose exposures ranged up to 23 mSv and an additional 21 workers received elevated doses when draining the precipitation tank. Seven workers immediately outside the plant received doses estimated at 6–15 mSv (combined neutron and gamma exposure). The three operators' estimated doses were: 5.4 Gy of neutrons and 8.5 Gy of gamma for patient A, 2.9 Gy of neutrons and 4.5 Gy of gamma for patient B, and 0.81 Gy of neutrons and 1.3 Gy of gamma for patient C [114–116]. The victim having the highest radiation exposure dose, received peripheral blood stem cell transplantation with identical human leukocyte antigen. Hematopoietic factors such as G-CSF (100 μg/day), EPO, TPO and blood components were administered as needed [116]. The patient developed severe radiation skin damage, gastrointestinal bleeding, and respiratory failure due to pulmonary edema and on day 58 he had a cardiopulmonary arrest and subsequently died on day 82 of multiple organ failure. The second victim received G-CSF 5 μg/kg/day for 4 days before umbilical cord blood transplant on day 8 and then 10 μg/kg/day till day 16). His bone marrow recovered 2 months after the accident. On day 153 he developed methicillin-resistant *Staphylococcus aureus* pneumonia that led to acute respiratory distress syndrome. He also developed a Cytomegalovirus infection and CI bleeding on day 145 and died on day 210 due to multiple organ failure. The third victim was not as close to the source as the two other victims had been. He was administered G-CSF (4.5–7.4 μg/kg/day) until day 28. His neutrophils reached a nadir on day 20. His platelets had decreased slower than the other 2 victims but still necessitated platelet transfusions on days 17, 20, and 23. He left the hospital on day 82 and survived [114,115].

7.10. Radiography pigtail source accident, Yanango, Peru, 1999

On 20 February 1999 [104,117,118], a radiological accident occurred when a welder picked up the unshielded 192Ir radiography pigtail source and placed it in his pocket. He kept this source in his pocket for several hours. This resulted in his receiving a high radiation dose that eventually necessitated the amputation of one leg. At night he went home and unknowingly exposed his wife and children to radiation but to a much less extent. At the time of the accident the source was 37 Ci [117]. According to three different center measurements, the welder's estimated doses to the femur and skin were between 9.966–11.752 Gy and 80–143 Gy, respectively [104,118].

On day 34 the patient's neutrophils dropped to 1,440/mm³, and total leucocytes to 1,500/mm³. GM-CSF was initiated on day 35 at 300 μg/day and continued until day 42, when there was a significant rise in WBCs. G-CSF was administered on day 34 post-exposure until day 42 post-exposure: the patient ultimately survived. It is inconclusive whether his treatment had a beneficial effect. Though the bone marrow did improve, administration was during a time when spontaneous recovery would have occurred [118].

7.11. Teletherapy radiation accident, Samut Prakan, Thailand, 2000

A radiation accident occurred during the January–February time-frame of 2000 in Thailand's Samut Prakan province [119,120]. The accident occurred when an insecurely stored, unlicensed 192Ir radiation source (425 Ci) was recovered by scrap metal collectors who, together with other workers, dismantled the container, unknowingly exposing themselves and others nearby to ionizing radiation. Over the following weeks, those exposed developed symptoms of radiation sickness and eventually sought medical attention. Ten victims presented with symptoms of vomiting. Total-body doses were estimated to range from 1 Gy to > 6 Gy. Four individuals were found to have received > 6 Gy. Nine victims who received 2 Gy or more were treated with both G-CSF and GM-CSF [119,120]. G-CSF administration was started at 250 or 500 μg/day (5–10 μg/kg/day) and in some cases increased to 1,000 μg/day (20 μg/kg/day), if WBCs remained low. GM-CSF started at 300 μg/day and was increased to 500 or 600 μg/day, depending on the response of the WBCs. Both G-CSF and GM-CSF were stopped if the WBC counts improved. Despite these efforts, victims died on days 38, 47, and 53 post-radiation exposure.

7.12. Radiography source accident, Meet Halfa, Egypt, 2000

On 5 May 2000 [121,122], a resident of Meet Halfa village found an industrial gamma radiography source (192Ir) that had been lost earlier. Not knowing that the item was a radioactive source, he took it to his home and shared it with his wife, sister, 2 sons and 2 daughters. The family believed the source to be a precious metal and handled it occasionally over the following weeks. On June 5, the 9-year old younger son died and was found to have marked bone marrow failure and extensive inflammatory skin lesions. On June 10, a fact-finding mission from the Ministry of Health found that 4 other members of the family had similar signs and symptoms [121]. On June 16, the father died with bone marrow failure and extensive skin lesions. On June 25 authorities discovered higher levels of radiation in the family home. By June 28 a source was found and identified as 192Ir. The half-life of 192Ir is 74 days. Calculating the decay process, the source activity would have been 31.5 Ci on the day the source came into the possession of the family. The estimated protracted whole-body radiation exposure doses for father (60 yr) and younger son (9 yr) were 7.5–8 Gy and 5–6 Gy, respectively (both died) [122]. Doses for the remaining five family members were 3.5–4 Gy. The five remaining family members were treated with filgrastim (10 μg/kg/day) and all survived.

7.13. Radiography equipment accident, Nueva Aldea, Chile, 2005

This accident occurred on 14 December 2005 at a cellulose plant under construction in Nueva Aldea [123]. Concepción, Chile. A radioactive source containing 192Ir fell out of gamma radiography equipment being used at a construction site near 3 workers. At the time of the accident the activity of the source was 90 Ci. Worker 1 was determined to have received a total-body dose of 1.3–1.5 Gy, and a dose of up to 1.600 Gy to the surface of his buttocks adjacent to a pocket where he had placed the source. Workers 2 and 3 were estimated to have received < 0.5 Gy whole-body doses [123]. Biodosimetry also was performed from blood samples on 34 individuals who had worked near the exposed source. One of these workers was calculated to have received 0.17 Gy and the remaining 33 workers received < 0.1 Gy.

Only one worker (#1) was admitted to a hospital and treated with G-CSF (10 μg/kg/day) on 18 December 2005. After collecting and analyzing hematological and radiological information that had not been available at the commencement of G-CSF administration, an IAEA report deemed that G-CSF administration was not
justified due to the level of the whole body radiation dose and the inhomogeneous character of the exposure. G-CSF administration was ceased on December 20, 2005 and the patient was given an experimental treatment with surgical excision followed by two administrations of mesenchymal stem cells for his local injury. Within 3 months, the wound on his buttocks had almost healed completely [123].


On 11 March 2006 [99], in the city of Fleurus (Belgium), an alarm went off in a facility used for the sterilization of medical devices. An operator entered the irradiation room to close the open cell door. The 60Co sources [activity: 2.96 × 10^15 Bq (800,000 Ci), dose rate ~ 5,000 Gy h⁻¹] were partly out of the security position at that time. As a consequence, the operator’s whole body was exposed to this source for about 22 s with a whole-body radiation dose estimated at 4.2–4.8 Gy with a range to different parts of the body of 1.5–6.4 Gy. Eighteen days after the incident, the operator consulted a physician and was diagnosis of accidental radiation exposure. He was found to have hematological syndrome with a 26% drop in hemoglobin, a platelet nadir of 2,000/mm², and a leukocyte nadir of 400/mm³. Eight days after hospitalization he developed septicemia. Treatment with pegylated G-CSF (6 mg/day) was initiated on day 28 after exposure. On days 32 and 33 post-exposure, the victim received pegylated EPO and recombinant human stem cell factor (SCF). Cytokines had an immediate effect and the victim had complete resolution of the hematopoietic syndrome by day 43 [99].

7.15. Iridium radiation device accident, Dakar, Senegal, 2006

In June–August 2006 [99], an industrial radiation device with 192Ir was used but its source did not properly retract into its shielded container. It was later discovered that the source was not secured properly. It was estimated that 63 people had received radiation from the source. The most severely exposed victim was admitted to a hospital in France on 25 August 2006. He was found to have a leukocyte nadir of 700/mm³ and a platelet nadir of 8,000/mm³. Radiation dose reconstruction estimated that the mean dose was 3.4 Gy, but with a very wide range of doses to specific parts of the body; e.g., 1.3 Gy to the liver and up to 75 Gy to the skin of the left arm. He was diagnosed with hematopoietic syndrome with a severe cutaneous syndrome. Treatment was initiated with pegylated G-CSF (6 mg/day), recombinant SCF, and pegylated EPO. The patient rapidly recovered to normal blood counts but cutaneous syndrome required additional medical treatments [99].

7.16. Radiation accident, Mayapuri, Delhi, India, 2010

In March 2010 [124–127], the locality of Mayapuri was affected by a serious radiological accident; an Atomic Energy of Canada Limited gammacell 220 research irradiator, owned by Delhi University since 1968 but unused since 1985, was sold at auction to a scrap metal dealer on 26 February 2010. The orphan source arrived at a scrap yard in Mayapuri, where it was dismantled on March 12 by workers unaware of the hazardous nature of the device. The 60Co source was cut into 11 pieces. The smallest of the fragments was taken by the owner, who kept it in his wallet; two fragments were moved to a nearby shop, while the remaining eight remained in the scrap yard. All of the sources were recovered by mid-April and transported to the Narora Atomic Power Station, where it was claimed that all radioactive material originally contained within the device was accounted for. Eight people were hospitalized as a result of radiation exposure, where one died [124].

Within a week of incidence, the dealer displayed skin hyperpigmentation of the hands and forearm, loss of scalp hair, nausea and fatigue. With these clinical signs, symptoms and history, he was diagnosed as a case of suspected radiation injury. This patient received repeated transfusions of platelets and packed red blood cells, fluids, and treated with antibiotics and a systemic antifungal agent. He also was treated with G-CSF (5 µg/kg). His exposure dose as calculated during the course of treatment was 3.1 Gy. He did not respond to the treatment and died on 26 April 2010, within 6 weeks of exposure. It is important to note that his treatment started 5 weeks after exposure [124]. Seven other persons working in the shop during that period also were traced. Of those traced, five individuals developed skin manifestations and fatigue. Based on blood biomarkers, the deceased victim and the additional four exposed individuals demonstrated signs of acute radiation exposure [125]. Two exposed victims were treated with G-CSF and they survived. Unfortunately, the publication containing the details of the treatment of this accident victims [126] was retracted by the authors [127].

There have been a number of radiation incidents since 1986 (Hanoi, Vietnam, 1992; Tomsk, Russia, 1993; Tammiku, Estonia, 1994; San Jose, Costa Rica, 1996; Lilo, Georgia, 1997; Sarov, Russia, 1997; Panama, 2000; Cochabamba, Bolivia, 2002; Shandong Jining, China, 2004; London, UK, 2006; Turmero, Venezuela, 2010; Fukushima, Japan, 2011) where CSFs were not used because victims either did not have significant myelosuppression or for other reasons [23].

8. Summary and conclusion

The published results with G-CSF and GM-CSF using various animal models of hematopoietic ARS suggest consistent radioprotective efficacy for survival and blood leukocyte recovery across species. The efficacy is dependent on the dose of CSF [73], treatment schedule [67,75], duration of the treatment [68,82,84], animal strains/source [73] and radiation dose [68,75], but largely independent of the radiation source. There are significant shortcomings in some studies in relation to design (small sample size for canines, minipigs, and NHPs), lack of concurrent controls in some studies, insufficient information regarding supportive care, euthanasia criteria, inadequate animal pharmacokinetics data for human dose conversion [82], difficulty in verifying data accuracy/integrity/adequacy (non-good laboratory practice studies), and interpretation. These experimental deficiencies tend to limit the usefulness of some studies presented above. However, despite some of the limitations of the published works, the aggregate results of these publications support the concept that rhG-CSF treatments provide a significant hematopoietic recovery and, in turn, survival for individuals with ARS.

Treating radiation injuries is a complicated process. In the majority of radiation accidents, radiation exposure is un-uniform, resulting in a sparing of portions of the bone marrow. Therefore, stimulating the victim’s own spared hematopoietic elements with the use of CSF is a promising strategy. The general conclusion by several investigators and clinicians is that CSF improves blood leukocyte levels and for some victims this may prove to be life-saving. Others suggest however, that G-CSF and GM-CSF treatments may adversely affect blood platelet counts so the IAEA recommends that platelet counts be monitored when G-CSF is being administered [110]. Further, it needs to be noted that G-CSF, alone or in combination with other cytokines or chemotherapeutic agents, has been shown to increase cell cycle entry by murine and human hematopoietic stem cells, a state that reduces their repopulating efficiency following transplantation [128]. This may be relevant
when considering the use of G-CSF and possibly GM-CSF in ARS patients that also receive BMT.

Among radiation incident victims from 1986 to the present, more than 51 individuals have been treated with recombinant CSFs following accidental radiation exposures. Results from various treatments are hard to interpret. The number of victims who received CSF was small for each accident and CSF treatment usually started late after radiation exposure; in many cases the accident victims did not know they had been exposed to high doses of radiation until days after exposure. In general, the use of CSF appeared to be beneficial, and would have been more effective if administered earlier after radiation exposure. Results for the efficacy of CSF with radiation-induced myelosuppression are positive, but not conclusive, by any means. Recent studies with large animal models (NHP) clearly demonstrate the radioprotective efficacy of rhG-CSF treatments as well as capability of these recombinants to promote for hematopoietic recovery. Such experimental demonstrations strongly suggest their usefulness to radiation-exposed victims. The US FDA may approve G-CSF and GM-CSF for the management of radiation-induced aplasia in near future.

Declaration of Interest

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