

## Recent advances in post autologous transplantation maintenance therapies in B-cell non-Hodgkin lymphomas

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### Abstract

Lymphomas constitute the second most common indication for high dose therapy (HDT) followed by autologous hematopoietic cell transplantation (auto-

HCT). The intent of administering HDT in these heterogeneous disorders varies from cure (*e.g.*, in relapsed aggressive lymphomas) to disease control (*e.g.*, most indolent lymphomas). Regardless of the underlying histology or remission status at transplantation, disease relapse remains the number one cause of post auto-HCT therapy failure and mortality. The last decade has seen a proliferation of clinical studies looking at prevention of post auto-HCT therapy failure with various maintenance strategies. The benefit of such therapies is in turn dependent on disease histology and timing of transplantation. In relapsed, chemosensitive diffuse large B-cell lymphoma (DLBCL), although post auto-HCT maintenance rituximab seems to be safe and feasible, it does not provide improved survival outcomes and is not recommended. The preliminary results with anti-programmed death -1 (PD-1) antibody therapy as post auto-HCT maintenance in DLBCL is promising but requires randomized validation. Similarly in follicular lymphoma, maintenance therapies including rituximab following auto-HCT should be considered investigational and offered only on a clinical trial. Rituximab maintenance results in improved progression-free survival but has not yet shown to improve overall survival in mantle cell lymphoma (MCL), but given the poor prognosis with post auto-HCT failure in MCL, maintenance rituximab can be considered on a case-by-case basis. Ongoing trials evaluating the efficacy of post auto-HCT maintenance with novel compounds (*e.g.*, immunomodulators, PD-1 inhibitors, proteasome inhibitors and bruton's tyrosine kinase inhibitors) will likely change the practice landscape in the near future for B cell non-Hodgkin lymphomas patients following HDT and auto-HCT.

**Key words:** Mantle cell lymphoma; Diffuse large B cell lymphoma; Follicular lymphoma; Autologous hematopoietic cell transplantation

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**Core tip:** Prevention of disease-relapse is an unmet medical need in B-cell non-Hodgkin lymphomas (NHL) undergoing autologous hematopoietic cell transplantation (auto-HCT). In this review, are summarized potentially paradigm changing advances in post auto-HCT, maintenance strategies in B-cell NHL.

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## INTRODUCTION

Hodgkin and non-Hodgkin lymphomas (NHL) collectively constitute the second most common indication for high dose therapy (HDT) and autologous hematopoietic cell transplantation (auto-HCT)<sup>[1]</sup>. In chemotherapy responsive relapsed lymphoid malignancies auto-HCT can provide long-term disease control, while avoiding the immunologic complications and delayed immune reconstitution associated with allogeneic HCT.

The curative potential of auto-HCT or the expected duration of disease control in lymphoid malignancies varies depending on the histological subtype, number of prior therapy lines and depth of remission prior to HDT. The role of auto-HCT as a potentially curative option in relapsed, chemosensitive diffuse large B-cell lymphoma (DLBCL) is well-defined. The PARMA trial<sup>[2]</sup> established that salvage chemotherapy and auto-HCT provided a significantly better event-free survival (EFS) and overall survival (OS) in subjects randomized to the HDT arm. Several registry based<sup>[3-6]</sup> and prospective studies in the rituximab-era<sup>[7]</sup> have reproduced these results. In contrast, auto-HCT when applied upfront for mantle cell lymphoma (MCL)<sup>[8]</sup>, or for relapsed, chemosensitive patients with follicular lymphoma (FL) is generally not considered a curative modality.

Regardless of the underlying histology or remission status at transplantation, disease relapse or progression remains the number one cause of post auto-HCT therapy failure and mortality. Prevention of disease relapse following auto-HCT in lymphoid malignancies therefore remains an unmet medical need. Disease relapse following auto-HCT occurs *via* two possible mechanisms. Most patients relapse likely due to the proliferation of a resistant clone of lymphoma cells (or stem cells) surviving the HDT. A minority may experience relapse due to re-infusion of an autograft contaminated by lymphoma cells<sup>[9]</sup>. In order to circumvent the problem of autograft contamination by lymphoma cells, several studies have examined the role of *ex vivo* purging (by monoclonal antibodies, CD34<sup>+</sup> cell selection, *etc.*)<sup>[10,11]</sup> and *in vivo* purging (*e.g.*, rituximab with mobilization)<sup>[12,13]</sup> of autologous stem cell products. However, randomized

data do not demonstrate improved outcomes with purged auto-HCT<sup>[14]</sup>. Similarly intensifying HDT with radioimmunotherapy based conditioning regimens<sup>[15]</sup> have likewise not demonstrated improved HCT outcomes. A handful of studies have looked at tandem auto-HCT following by reduced-intensity allogeneic HCT in lymphoid malignancies<sup>[16,17]</sup>. However no randomized data are available to support the use of this approach. Moreover advanced age, comorbidities and suitable donor availability makes such a tandem HCT approach theoretically applicable to only a small subset of lymphoma patients.

Over the last decade several studies have shown improved outcomes with maintenance immunotherapies applied after conventional chemoimmunotherapies in patients with lymphoid malignancies<sup>[18-20]</sup>. Owing to the excellent safety profile of maintenance immunotherapies in the non-transplant setting, this modality has now been investigated post auto-HCT in lymphoid malignancies. In this article we review the role of post auto-HCT maintenance therapies in B cell NHL, along with overview of novel agents that likely will serve as future maintenance strategies in the post auto-HCT setting.

## DIFFUSE LARGE B CELL LYMPHOMA

Of DLBCL patients who relapse after auto-HCT, a vast majority relapse early post-transplant. In a recent Center for International Blood and Marrow Transplant Research (CIBMTR) study<sup>[5]</sup>, nearly three quarter of relapses in DLBCL were seen within the first 9 mo following autoHCT. A landmark analysis of DLBCL patients surviving the first 9 mo post-transplant without relapse/progression, showed a 5-year progression-free survival (PFS) probability of > 80%, suggesting that an effective strategy to prevent early DLBCL relapses post auto-HCT would theoretically translate into significant improvements in patient outcomes.

Studies evaluating the role of maintenance therapies in DLBCL are summarized in Table 1<sup>[21-26]</sup>. A small case series by Lim *et al*<sup>[21]</sup> ( $n = 15$ ) provided preliminary evidence for maintenance in DLBCL post HCT. In this study post auto-HCT rituximab maintenance in high risk NHL for 2 years (once every 3 mo) provided a relapse-free survival of 100% and OS of 80% at 5.5 years (Table 1). Subsequently, in a small prospective study ( $n = 12$ ), *in vivo* graft purging and post auto-HCT maintenance with rituximab in high risk DLBCL resulted in 3 year PFS of 83% and OS of 100%<sup>[22]</sup>.

These studies paved way for a large prospective randomized study, in which high-risk DLBCL ( $n = 269$ ) patients after undergoing an upfront autoHCT consolidation in first remission, were randomized to a brief rituximab course (four weekly doses) *vs* observation. In patients who achieved a complete remission (CR) following HDT, this brief maintenance rituximab exposure provided statistically significant superior EFS (Table 1)<sup>[24]</sup>. Since all DLBCL patients underwent an auto-HCT

**Table 1** Studies evaluating the role of antibody based maintenance therapy post autologous hematopoietic cell transplantation in diffuse large B cell lymphoma

Ref.	Study design	Maintenance schedule	n	% CS at HCT	PFS/EFS (%)	OS (%)	Comments
Lim <i>et al</i> <sup>[21]</sup>	Retrospective	Rituximab 375 mg/m <sup>2</sup> (q 3 mo for a total of 8 doses)	15	100	-	80 (5.5 yr)	Relapse free survival 100% (5.5 yr)
Zhang <i>et al</i> <sup>[22]</sup>	Single arm prospective	Rituximab 375 mg/m <sup>2</sup> (q 3 mo for 2 yr)	12	100	83 (3 yr)	100 (3 yr)	Prolonged hypogammaglobinemia in 2 patients
Tsirigotis <i>et al</i> <sup>[23]</sup>	Retrospective	Rituximab 375 mg/m <sup>2</sup> (80% q wk and 20% q mo)	19	79	NR	NR	Compared to controls, maintenance improves PFS and OS
Haioun <i>et al</i> <sup>[24]</sup>	Randomized prospective	Rituximab 375 mg/m <sup>2</sup> (weekly for 4 doses)	269 R = 139, O = 130	84.5	80 (R) vs 71 (O) (4 yr)	-	Patients underwent autoHCT upfront in first remission
Gisselbrecht <i>et al</i> <sup>[25]</sup>	Randomized prospective	Rituximab 375 mg/m <sup>2</sup> (q 8 wk for 1 yr)	242 R = 122, O = 120	100	52 (R) vs 56 (O) (4 yr)	61 (R) vs 65 (O) (4 yr)	4 yr EFS was 52% for Rituximab arm while 53% for observation arm
Armand <i>et al</i> <sup>[26]</sup>	Prospective phase II	Pidilizumab 1.5 mg/kg (q 42 d for 3 cycles)	66	91	72 (16 mo)	85 (16 mo)	ORR was 51% (CR of 34%) in pts with measurable disease after autoHCT

CS: Chemo-sensitive; PFS: Progression free survival; OS: Overall survival; NR: Not reached; R: Rituximab arm; O: Observation arm; EFS: Event free survival; ORR: Overall response rate; CR: Complete remission; HCT: Hematopoietic cell transplantation.

in first remission in this trial (a scenario that would not be considered standard-of-care today), caution must be exercised in extrapolation of these data to relapsed DLBCL patients undergoing auto-HCT. Of note, quality of life (QOL) assessments in this study showed rapid recovery (as early as day 100) in all the tested QOL subdomains after auto-HCT and rituximab maintenance did not negatively influence the QOL outcomes<sup>[27]</sup>.

The more clinically relevant question of rituximab maintenance in DLBCL patients after failing first line therapies was addressed in the collaborative trial in relapsed aggressive lymphoma (CORAL) study. In this trial (after an initial randomization of patients between two different salvage therapies), a second randomization of relapsed DLBCL patients after auto-HCT to either rituximab maintenance (every 2 mo for 1 year) or observation alone was performed (Table 1). Rituximab maintenance in this study provided no benefit in terms of EFS, PFS or OS. However an unplanned subset analysis suggested a possible benefit of maintenance rituximab in female patients<sup>[25]</sup>. This finding likely is a reflection of less rapid rituximab clearance in females, which in turn leads to higher blood concentrations of rituximab<sup>[28]</sup>. This observation could suggest a benefit of rituximab post auto-HCT in female subjects (and possibly in males using higher doses of rituximab), but this hypothesis needs further investigation. In addition to a lack of randomized data supporting using of maintenance rituximab for relapsed DLBCL, uncontrolled data suggest prolonged hypogammaglobulinemia extending beyond 2 years when using this approach in the post auto-HCT setting<sup>[21,22]</sup>.

Advances in our understanding of tumor biology have led to the development of novel targeted therapies in DLBCL. Programmed death 1 (PD-1) is a T cell co-receptor that binds to the ligand B7 to maintain an

immunosuppressive tumor microenvironment. PD-L1 is expressed on suppressor immune cells in the tumor microenvironment and in a subset of DLBCL<sup>[29-32]</sup> where it may alter the composition and function of tumor-infiltrating lymphocytes<sup>[33]</sup>, and therefore represents a valid therapeutic target. Early after auto-HCT, a majority of the circulating leukocytes are natural killer cells, CD45RO+ memory/effector cells and monocytes, which comprise anti PD-1 monoclonal antibody target populations and whose presence has been associated with a favorable prognosis in DLBCL<sup>[34-36]</sup>. In DLBCL patients, post auto-HCT PD-1 blockade may prevent PD-1 mediated exhaustion of antitumor lymphocytes, leading to eradication of residual disease and improvement in transplant outcomes. In a multicenter phase II trial (Table 1) an anti-PD-1 monoclonal antibody, pidilizumab, was administered to patients with relapsed or refractory DLBCL following auto-HCT. The 16-mo PFS was 72% in the overall population and 70% in the subgroup of high-risk patients who had a positive positron emission tomography scan at the end of salvage therapy. Remarkably, 51% of patients with residual disease after transplant responded to the treatment, and 34% of these patients had CR without significant autoimmune toxicity<sup>[26]</sup>. Although promising, these results have not been confirmed in a prospective randomized trial yet.

Several ongoing trials are looking at maintenance post auto-HCT in DLBCL using immune modulators (NCT01241734; lenalidomide maintenance; phase I / II), PD-1 inhibitors (NCT02362997; pembrolizumab; phase II), proteasome inhibitors (NCT00992446; bortezomib in combination with vorinostat; phase II) and Bruton's tyrosine kinase inhibitors<sup>[37]</sup> (ibrutinib maintenance in activated B-cell type DLBCL in the soon to open BMT-CTN/Alliance phase III study).

**Table 2** Studies evaluating the role of rituximab maintenance after autologous hematopoietic cell transplantation in mantle cell lymphoma

Ref.	Design	Maintenance	n	% CS at HCT	PFS/EFS (%)	OS (%)	Comments
Lim <i>et al</i> <sup>[46]</sup>	Retrospective	Rituximab 375 mg/m <sup>2</sup> (q 3 mo for 2 yr starting day + 100)	8	100	57	67	Delayed immunoglobulin reconstitution was seen in all patients and persisted beyond the rituximab maintenance period
Graf <i>et al</i> <sup>[47]</sup>	Retrospective	Rituximab 375 mg/m <sup>2</sup> (variable dosing schedule but median doses = 8)	157 R = 50, O = 107	Almost all the patients who received MR	HR of 0.33	HR of 0.40	In the landmark analysis at D 100 after auto-HCT 3 yr PFS and OS were statistically better in the MR compared to the no MR group
Dietrich <i>et al</i> <sup>[48]</sup>	Retrospective	Rituximab 375 mg/m <sup>2</sup> (every 3 mo for 2 yr)	72 R = 22, O = 50		90 (R) vs 65 (O)	90 (R) vs 84 (O)	Patients in both the arms were well matched. The median observation time was 56 mo
Gouill <i>et al</i> <sup>[49]</sup>	Prospective phase III	Rituximab 375 mg/m <sup>2</sup> IV (every 2 mo for 3 yr)	238 R = 119, O = 119	81.4	93.2 (R) vs 81.5 (O) (2 yr)	93.4 (R) vs 93.9 (O) (2 yr)	All patients received 4 courses of R-DHAP followed by auto-HCT. The conditioning regimen of auto-HCT was R-BEAM (R=500 mg/m <sup>2</sup> )

CS: Chemo-sensitive; PFS: Progression free survival; EFS: Event free survival; OS: Overall survival; MR: Maintenance rituximab; HR: Hazard ratio; R: Rituximab arm; O: Observation arm; R-DHAP: Rituximab, dexamethasone, cytarabine and cisplatin; R-BEAM: Rituximab, carmustine, etoposide, cytarabine and melphalan; HCT: Hematopoietic cell transplantation.

### Bottom-line

Although rituximab seems to be a feasible and safe option post auto-HCT, it does not provide improved disease control or survival outcomes and is not recommended in this setting. The preliminary results with PD-1 antibody as a post auto-HCT maintenance therapy in DLBCL are promising but require validation in a randomized setting.

## FOLLICULAR LYMPHOMA

Registry data from the European Group for Blood and Marrow Transplantation (EBMT)<sup>[38]</sup> and the CIBMTR show no plateau in relapse rates of FL after auto-HCT<sup>[39]</sup>. Since maintenance immunotherapies (with rituximab) in FL have shown benefit after both frontline<sup>[18]</sup> and subsequent chemoimmunotherapies<sup>[40,41]</sup>, the application of rituximab maintenance following auto-HCT would also be a reasonable strategy to potentially prevent relapse.

The EBMT recently reported the efficacy and safety of rituximab, as *in vivo* purging before transplantation and as maintenance treatment immediately after HDT and auto-HCT in patients with relapsed FL, in a randomized prospective trial. In this study, 280 rituximab-naïve patients with relapsed FL were randomly assigned to auto-HCT with or without *in vivo* rituximab purging, followed by a second randomization to rituximab maintenance therapy (once every 2 mo for a total of four infusions) or observation<sup>[42]</sup>. At a median follow-up of 8.3 years, rituximab maintenance when compared to observation resulted in superior PFS at 10 years (54% vs 37%), but did not translate into an improvement in OS (73% vs 68%)<sup>[42]</sup>. In addition, maintenance rituximab was associated with a higher (albeit statistically non-significant) rate of late neutropenia. Considering the fact that this study enrolled rituximab-naïve patients, the lack of a survival benefit in this study is particularly noteworthy. It is plausible that the relatively short maintenance schedule employed in this trial resulted in

a lack of survival benefit. Though randomized trials in FL in the non-transplant setting have shown no OS or PFS benefit with rituximab maintenance when using a shorter course (about 8 mo) of maintenance, as used in the EBMT study<sup>[43]</sup>, the Swiss study [Swiss Group for Clinical Cancer Research (SAKK 35/98)] demonstrated superior EFS<sup>[44]</sup>.

While rituximab maintenance post auto-HCT appears unlikely to improve survival of FL patients, the role of other novel approaches as maintenance therapies post auto-HCT in follicular lymphoma warrants further investigation. Ongoing post auto-HCT maintenance clinical trials involving FL patients are evaluating the role of immune modulators (NCT01035463; lenalidomide maintenance; phase I / II), and proteasome inhibitors (NCT00992446; bortezomib in combination with vorinostat; phase II) as maintenance options.

### Bottom-line

Maintenance therapies including rituximab following autoHCT should be considered investigational in patients with FL and should only be offered on a clinical trial.

## MCL

Maintenance rituximab after induction chemoimmunotherapies has been shown to improve OS in older patients with MCL<sup>[20]</sup>. In MCL, prevention of relapse or progression after auto-HCT is crucial; since outcome after auto-HCT relapse is dismal with a median survival of only 23 mo<sup>[45]</sup>. Several retrospective and a few prospective studies have evaluated the potential role of post auto-HCT maintenance rituximab in MCL (Table 2)<sup>[46-49]</sup>.

Dietrich *et al*<sup>[48]</sup> compared post auto-HCT maintenance rituximab (administered within a prospective phase II study of rituximab maintenance in B-cell lymphoma NCT 01933711), to MCL patients getting no maintenance (but transplanted during the same

**Table 3** Future directions - drugs that are currently studied in relapsed/refractory aggressive and indolent B cell lymphomas that can potentially be studied in the post autologous hematopoietic cell transplantation setting

Drug	Mechanism of action	Ongoing trials in relapsed/refractory aggressive and indolent B cell lymphomas (not in post auto-HCT setting)
CD-19 antibodies (MEDI-551)	IgG1k antibody-dependent cellular cytotoxicity enhanced anti-CD19 mAb	Phase I (NCT00983619) Phase II (with ICE/DHAP NCT01453205) Phase II (with PD-1 inhibitor NCT02271945)
MPDL3280A	Targets PD-L1 expressed on tumor cells and tumor-infiltrating immune cells	Phase I (with Obinutuzumab NCT02220842)
Polatuzumab vedotin	Antibody-drug conjugate that targets CD 79b on the B cell receptor complex	Phase II (with Rituximab or Obinutuzumab and Bendamustine NCT02257567)
Obinutuzumab (GA101)	Fully humanized IgG1 mAb that selectively binds to the extracellular domain of the human CD20 antigen on malignant human B cells	Phase I b/ II (with lenalidomide NCT01582776) Phase I b/ II (with lenalidomide NCT01995669)
Veltuzumab	A fully humanized mAb directed against the CD20 antigen.	Phase I / II (NCT01147393)
ABT-199	Oral selective small molecule inhibitor of the anti-apoptotic protein Bcl-2	Phase I (NCT02055820) Phase I (with BR NCT01594229) Phase II (with BR vs BR alone NCT02187861)
Alisertib	Oral selective small molecule inhibitor of the serine/threonine protein kinase Aurora A kinase	Phase I (with Romidepsin NCT01897012) Phase I (with Vorinostat NCT01567709) Phase I (with Bortezomib and Rituximab NCT01695941)
SAR245409	Oral small molecule targeting the PI3K and mTOR kinases.	Phase II (with +/- Rituximab NCT01812005)
Belinostat	HDAC inhibitor	Phase I / II (NCT01587040) Phase I (with Carfilzomib NCT02142530) Phase II (with Ibritumomab Tiuxetan NCT01686165)

ICE: Ifosfamide, carboplatin and etoposide; DHAP: Dexamethasone, high dose cytarabine, cisplatin; PD-1: Programmed death-1; BR: Bendamustine, rituximab; mAb: Monoclonal antibody; PI3K: Phosphatidylinositol 3 kinase; mTOR: Mammalian target of rapamycin.

time period of aforementioned trial). The study showed that the 2 year PFS was significantly better in the maintenance rituximab compared to no maintenance rituximab cohort (90% and 65% respectively  $P = 0.014$ ) with no difference in OS between the two arms (90% in maintenance rituximab and 84% in no maintenance rituximab) (Table 2). However, following a multivariate adjustment for other factors maintenance rituximab was strongly associated with both PFS and OS<sup>[48]</sup>.

The only randomized phase III trial to study maintenance therapy in post auto-HCT setting in MCL was conducted by the LYSA, GOELAMS (Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang) and GELA (Groupe d'Etude des Lymphomes de l'Adulte). Patients who achieved a CR or partial remission to auto-HCT ( $n = 238$ ) were randomized to maintenance rituximab ( $n = 119$ ) (375 mg/m<sup>2</sup>, IV every 2 mo for 3 years) or wait and watch (WW) ( $n = 119$ ) arms. The 2 year EFS and PFS were statistically different between the two arms ( $P = 0.015$  for both) favoring the maintenance rituximab (93.2% in the maintenance rituximab arm vs 81.5% in the WW arm), however there was no difference in OS (93.4% in the maintenance rituximab arm vs 93.9% in the WW arm) (Table 2)<sup>[49]</sup>. Final data with mature follow up and complete toxicity assessment is not yet reported.

Among lymphoid malignancies, the therapeutic landscape of MCL is rapidly changing with several new agents approved for therapy in relapsed/refractory setting in the last 2-3 years. Lenalidomide has shown significant activity in relapsed/refractory MCL leading to

its approval as a single agent in this patient group<sup>[50]</sup>. Fondazione Italiana Linfomi ongoing randomized phase III study is evaluating the role of lenalidomide maintenance after upfront auto-HCT consolidation in MCL (NCT02354313). Ibrutinib, another agent with known activity in relapsed MCL<sup>[51]</sup> is a potential candidate for post auto-HCT maintenance. A single arm prospective trial is administering ibrutinib as maintenance therapy after intensive induction programs (with or without auto-HCT) (NCT02242097). Minimal residual monitoring (MRD) monitoring with polymerase chain reaction (PCR) for immunoglobulin heavy chain (IgH) and/or bcl-1 rearrangement was employed in the MCL-2 trial<sup>[52]</sup>. Pre-emptive treatment with rituximab achieved a second molecular remission in 92% of the patients ( $n = 26$ ) experiencing molecular relapse (PCR+ for IgH rearrangement) post auto-HCT. After pre-emptive treatment median clinical and molecular relapse free survivals were 3.7 and 1.5 years respectively. Though strictly speaking pre-emptive therapy is not post-transplant maintenance, it is akin to the post auto-HCT maintenance therapy but needs further investigation.

### Bottom-line

Considering the poor prognosis to post auto-HCT failures in MCL, rituximab maintenance should be evaluated on a case-by-case basis (*e.g.*, patients who would not be fit for a subsequent allogeneic transplant). In addition, rationale application of novel maintenance therapies using MRD monitoring represents a promising investigational approach for MCL patients after auto-HCT.

## ON THE HORIZON

Moving forward, to further improve outcomes for NHL patients undergoing auto-HCT, efforts need to be focused on evaluating novel consolidation or maintenance strategies, possibly with agents not used in induction chemoimmunotherapies. Table 3 summarizes the novel agents that are currently being studied in relapsed/refractory aggressive and indolent B cell NHL. Consolidation and/or maintenance with monoclonal antibodies [to cite a few - anti CD 79b (Polatuzumab Vedotin), anti CD19 (MEDI 551) and anti CD20 (Obinutuzumab and Veltuzumab)], HDAC inhibitors (Belinostat), PDL-1 inhibitors (MPDL3280A), Bcl-2 inhibitors (ABT-199), Aurora A kinase inhibitors (Alisertib) and mTOR/PI3K inhibitors (SAR245409) in the post auto-HCT setting seems to be a potential area of further investigation.

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