Tapering and Discontinuation of Thrombopoietin Receptor Agonist Therapy in Patients with Immune Thrombocytopenia: Results from a Modified Delphi Panel

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Abstract

Background: Recent evidence suggests that in patients with immune thrombocytopenia (ITP) with a stable response on thrombopoietin receptor agonists, treatment may be tapered and/or discontinued. ***Objectives:*** The objective of this study was to provide a guide for tapering and discontinuation of TPO-RA therapy in patients with ITP, based on hematologist survey results, existing evidence, and expert consensus. ***Patients/Methods:*** UK hematologists completed a survey to characterize self-reported practice patterns related to TPO-RA tapering and discontinuation in patients with ITP. Using a modified Delphi panel approach, ITP experts developed consensus statements regarding the use of TPO-RA tapering and discontinuation. ***Results:*** Survey respondents es-timated that 30–34% of their patients were suitable for ta-pering or discontinuation and that 29–35% of these patients required treatment re-initiation after an average treatment-free interval of 86–106 days. No clear predictors of patient suitability or response to tapering or discontinuation were identified. The ITP expert consensus was that approximately 30% of patients are eligible for tapering and discontinuation, which may be considered after 6–12 months for patients demonstrating an adequate treatment response (platelet count >50,000/μL at ≥75% of assessments in the preceding 6 months). Treatment re-initiation may be considered if the platelet count decreases or if the patient becomes symp-tomatic. Individual differences need to be taken into ac-count when considering TPO-RA tapering or discontinua-tion. ***Conclusions:*** Tapering and discontinuation of TPO-RA therapy may be considered for certain patients with ITP. Fur-ther study is needed to better predict patients likely to achieve sustained off-treatment responses after tapering and discontinuation.

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Published by S. Karger AG, Basel

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Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder resulting in reduced platelet production and increased platelet destruction [1]. Platelets and their precursors, megakaryocytes, are targeted by autoantibodies, leading to an increased risk of bleeding [2]. Diagnosis is based on a platelet count <100,000/μL, but platelet counts between 20,000 and 100,000/μL are associated with a lower risk of major bleeding events than are values <20,000/μL [1, 3]. Treatment is typically reserved for patients with platelet counts <20,000–30,000/μL, active bleeding, or a high risk of bleeding (e.g., patients undergoing surgery) [1, 3].

Thrombopoietin receptor agonists (TPO-RAs) induce proliferation and differentiation of megakaryocytes, thereby increasing platelet production [4]. Eltrombopag and romiplostim have been shown to improve platelet count and prevent major bleeding events in 80–90% of patients with ITP [5, 6] and may improve quality of life [7]. Response rates of 65–88% have been reported in long-term follow-up studies [8–10]. TPO-RAs are generally well tolerated by patients, even with long-term treatment [11]. Adverse events of romiplostim and eltrombopag reported in phase 3 trials were similar and generally mild; serious adverse events most frequently consisted of bleeding events in patients with low platelet counts [8, 12, 13]. Eltrombopag and romiplostim are approved by the European Medicines Agency and the US Food and Drug Administration for patients aged 1 year and above with primary ITP who are refractory to other treatments such as corticosteroids and immunoglobulins [14, 15].

The goal of TPO-RA therapy is not to normalize the platelet count but to elevate it to a level that minimizes the risk of bleeding, that is, a platelet count of 50,000–150,000/μL [14, 15]. For patients who can subsequently maintain a platelet count in the normal range without treatment, these agents will be titrated down. If, however, a platelet count >50,000/μL is considered safe, an additional question is whether some patients maintaining a platelet count of 50,000–150,000/μL on treatment can taper and stop their TPO-RA while maintaining their platelet level. Hematologists should evaluate their patients treated with TPO-RAs periodically and assess whether to continue TPO-RA treatment [14, 15].

Many patients require continuous TPO-RA therapy to maintain adequate platelet levels [16]. However, some patients may have sustained off-treatment responses after discontinuation of TPO-RA therapy [10, 17–24]. Various approaches to tapering and discontinuation of TPO-RA therapy have been used, and there is currently no consensus regarding the optimal approach [17, 21]. In addition, several questions remain regarding the identification of suitable patients for tapering and discontinuation, the expected duration of response after discontinuation, and methods for re-initiating therapy. Previous studies did not find any clinical or treatment characteristics that may predict a lasting response after treatment discontinuation [17, 19, 21, 22]. Červinek et al. [17] found higher rates of sustained off-treatment responses in patients requiring low TPO-RA doses, whereas no responses were seen in patients who required higher doses. Another study suggested that absolute immature platelet fractions may be a potential predictor of successful treatment termination [22]. However, sample sizes in these 2 studies were small. Finally, the definition of treatment response varied between studies, even though international definitions exist [25]. In the absence of a consolidated knowledge base, a practice survey was administered to UK hematologists and a modified Delphi panel process among ITP experts was hosted to consider consensus recommendations related to tapering and discontinuation of TPO-RA therapy in patients with ITP.

Methods

Survey of UK Hematology Practices
For the ITP expert consensus panel to consider the self-reported perspectives and experiences of practicing hematologists, a survey was designed and conducted. Survey methods considered appropriate best practices to optimize relevance and responsiveness for physician surveys [26, 27].

Hematologists and hematologic oncologists in practice for at least 3 years in the UK who had evidence of experience treating patients with TPO-RAs (based on prescribing practices) were included. A survey panel methodology was used to invite eligible hematologists to participate in a survey regarding their perceptions of and personal experience with tapering and discontinuation of TPO-RAs in patients with ITP (online suppl. Appendix 1; see www. karger.com/doi/10.1159/000510676 for all online suppl. material). Best practices in survey design were applied to avoid or minimize potential instrumentation bias or other sources of bias. A total of 495 hematologists were approached, with a target completion rate of 12% ($n = 60$), based on feasibility and time (1 week) for response. Descriptive statistics and content analysis were used to analyze responses.

ITP Expert Consensus Meeting
A live meeting was convened to synthesize evidence and practices related to TPO-RA tapering, discontinuation, and re-initiation among UK-based experts in the management of ITP. The ITP experts completed a pre-meeting survey (online suppl. Appendix 2) to establish their perspectives and experience related to the over-

all of TPO-RA tapering and discontinuation, identification of appropriate patients, expected outcomes after discontinuation, duration of off-treatment response, and unmet needs in supporting evidence that might prevent the development of recommendations.

In June 2017, seven ITP experts participated in a modified Delphi panel. This convenience sample of UK-based hematologists was put together for the panel using snowball referencing and was based on their expertise in the field and their experience with a larger number of patients with ITP. The meeting was supported by a structured technology-based platform to capture uninfluenced individual perspectives followed by a panel discussion where consensus among participants was sought. The online meeting platform enables anonymized collaboration through open data entry, surveying, and evaluations using ratings and rankings. The ITP experts also estimated the duration of TPO-RA discontinuation in their last 3 patients who had undergone TPO-RA tapering, discontinuation, and re-initiation of therapy. The meeting agenda included discussion regarding criteria for appropriate TPO-RA tapering and discontinuation as well as criteria for treatment re-initiation in patients who relapse after treatment discontinuation.

Results

Survey of UK Hematology Practices

The survey was completed by 49 of 495 hematologists (9.8%). Respondents had been in practice for an average of 12 years. Most were based in academic or teaching hospitals (84%), spending 86% of their time in direct patient care. Respondents reported managing an average of 47 patients with ITP over the past 6 months.

The number of respondents reporting experience with tapering and discontinuation of eltrombopag and romiplostim was 17 (35%) and 23 (47%), respectively. Survey respondents estimated that 30–34% of patients with ITP treated with TPO-RAs were suitable candidates for tapering or discontinuation. A stable platelet count was the most commonly cited reason for tapering and discontinuing treatment (58–76%), followed by a lack of or reduced risk of bleeding (17–24%; Table 1).

Survey respondents reported that 29–35% of their patients required re-initiation of treatment after discontinuing TPO-RA therapy. Treatment was re-initiated after a mean treatment-free interval of 86–106 days. The most commonly cited reason for treatment re-initiation was decreased platelet count (100%) followed by clinical symptoms (67–75%). The most common form of renewed treatment was TPO-RAs (Table 1). Hematologists reported that among their patients initially treated with eltrombopag, 44% received eltrombopag and 41% received romiplostim upon treatment re-initiation. Among those initially treated with romiplostim, 28% received el-

Table 1. Responses from 49 UK hematologists participating in the survey

Hematologist response, %	Eltrombopag	Romiplostim
Criteria used to define "well controlled" ITP for TPO-RA tapering and discontinuation		
Stable platelet count	58	76
Well-controlled symptoms or symptom-free	25	0
Lack of or reduced risk of bleeding	17	24
Reasons for treatment re-initiation		
Platelet count	100	100
Clinical symptoms	67	75
Other	20	0
Type of therapy used at treatment re-initiation		
Eltrombopag	44	28
Romiplostim	41	39
Other pharmacologic treatment	11	7
Surgery	6	4
Other nonpharmacologic regimen	2	1

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

trombopag and 39% received romiplostim when treatment was re-initiated.

Expert Consensus Meeting

Among the ITP experts, pre-meeting questionnaire responses indicated a high level of agreement that tapering of TPO-RA therapy can be a rational approach to ITP treatment and that discontinuation may be warranted in clinically improved patients who feel well. During the group discussion, several potential benefits of TPO-RA tapering and discontinuation were identified, including the possibility of treatment-free remission and increased patient convenience (Fig. 1).

ITP Expert Panel Opinion

- Tapering and discontinuation of TPO-RA therapy may be considered for certain patients.

The ITP experts agreed that a tapering approach may be considered after 6–12 months of treatment for patients with an adequate treatment response who are less likely to encounter a high-risk bleeding scenario. An adequate treatment response was defined as stable platelet count >50,000/μL in at least 75% of assessments in the preceding 6 months. Tapering should be done slowly. In patients with platelet levels <30,000/μL after tapering or discontinuing TPO-RAs, hematologists may consider a watch-

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Fig. 1. Potential benefits of TPO-RA tapering and discontinuation (expert opinion). TPO-RA, thrombopoietin receptor agonist.

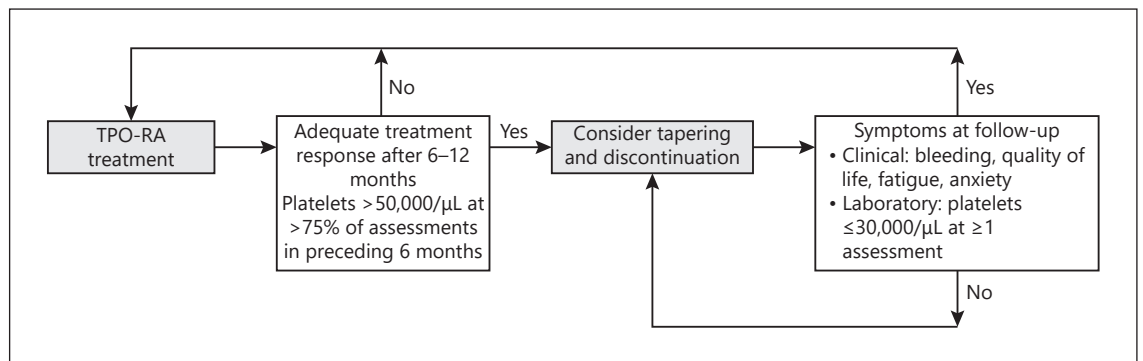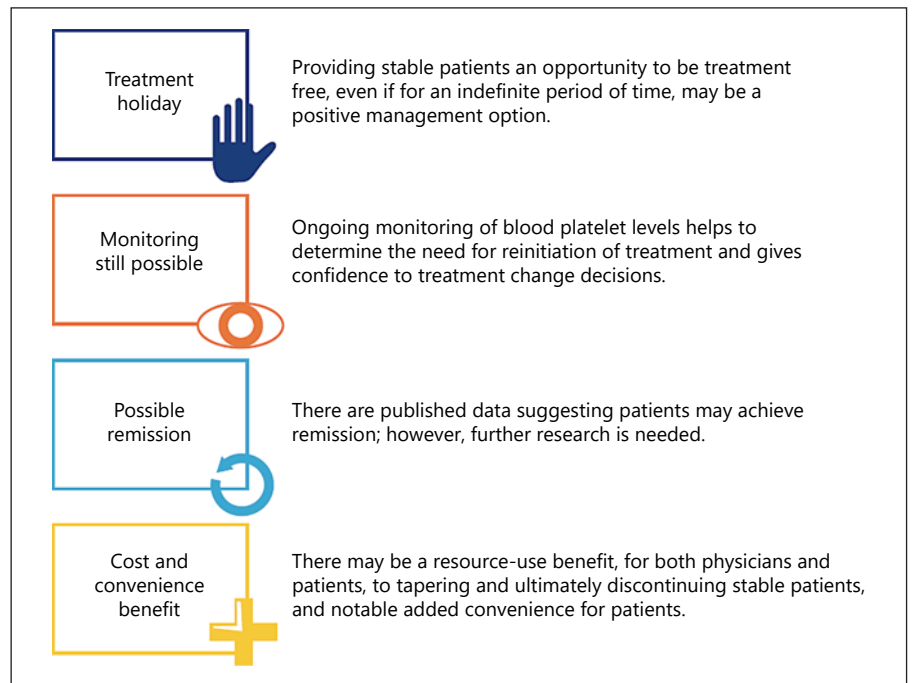|	
Treatment holiday	Providing stable patients an opportunity to be treatment free, even if for an indefinite period of time, may be a positive management option.
Monitoring still possible	Ongoing monitoring of blood platelet levels helps to determine the need for reinitiation of treatment and gives confidence to treatment change decisions.
Possible remission	There are published data suggesting patients may achieve remission; however, further research is needed.
Cost and convenience benefit	There may be a resource-use benefit, for both physicians and patients, to tapering and ultimately discontinuing stable patients, and notable added convenience for patients.

Fig. 2. TPO-RA tapering and discontinuation approach that can be considered for patients with primary ITP. ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

and-wait approach, maintaining the same dose level, to see if any bleeding occurs and check their platelet levels after a few weeks to account for natural fluctuations that occur, especially in patients treated with romiplostim. A flow chart of the suggested tapering and discontinuation approach is shown in Figure 2. The ITP experts also stressed that individual differences (e.g., asymptomatic chronically low platelet counts), patient preferences, and the impact of frequent testing on patients need to be taken into account when considering tapering and discontinuation of TPO-RA therapy, and benefits and risks should be considered carefully.

The ITP experts agreed that tapering or discontinuation may need to be reconsidered if the platelet count decreases to 30,000/μL or lower. Stopping tapering or restarting treatment may also need to be considered if patients experience bleeding and/or persistently worse quality of life due to anxiety, fatigue, or other factors related to ITP that could be alleviated by TPO-RA treatment.

ITP Expert Panel Opinion
- Tapering may be considered after 6–12 months for patients with an adequate treatment response.

Fig. 3. Patient characteristics that may be potential indicators of remission or relapse during tapering or discontinuation of TPO-RAs, based on expert opinion. ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

- An adequate treatment response was defined as stable platelet count >50,000/μL at ≥75% of assessments in the preceding 6 months.
- Tapering and discontinuation may need to be reconsidered if the platelet count decreases to ≤30,000/μL or if the patient experiences bleeding, persistently worse quality of life, anxiety, or fatigue associated with ITP that might be alleviated by resuming TPO-RA therapy.
- Individual differences and patient preferences should be taken into account.

According to the ITP experts, identifying suitable patients for tapering and discontinuation was one of the key challenges. At this time, it is not possible to predict with confidence which patients will achieve off-treatment responses, and how long treatment response will last. It was agreed that currently there are no clear predictive factors to help identify patients suitable for tapering. However, the ITP experts identified several factors that they would consider when deciding whether to taper or discontinue therapy (Fig. 3). These factors include age, disease duration, response, duration of treatment, current TPO-RA dose, platelet count, comorbidities, and concurrent use of other medication for ITP. Tapering and discontinuation may be considered especially in patients without bleeding events who are on a low dose of TPO-RAs.

Notably, the ITP experts also identified 2 primary factors that would make a tapering or discontinuation approach less appropriate: a history of severe or life-threatening bleeding and no effective rapid rescue therapy. Tapering or discontinuation may be less appropriate in case of a history of large fluctuations in platelet count, the presence of comorbidities that increase bleeding risk, concomitant use of anticoagulant or antiplatelet medications, and a history of rapid relapse after dose reduction. Continuing on a minimum dose or applying a step-wise titration over a longer period may be an appropriate tapering strategy for patients with fluctuating responses to treatment or in patients in whom responses to dose reductions need to be monitored relatively frequently. The ITP experts believe this will reduce the risk of withdrawal effects and maintain stability for the patient.

ITP Expert Panel Opinion
- There are no clear predictive factors to help identify patients who may be suitable for tapering and discontinuation.
- When deciding whether to taper or discontinue TPO-RA therapy, factors related to the patient (age), disease duration, and treatment (prior response to TPO-RA) may need to be taken into account.
- Situations in which tapering may not be appropriate include patients with a history of severe or life-threatening bleeding and the lack of effective rapid rescue therapy.

According to the ITP experts, the average duration of TPO-RA discontinuation, based on their last 3 patients, was 2–3 months. The longest reported treatment-free interval estimate was 4–5 years. The ITP experts reported that 34.7% of patients who discontinued eltrombopag and 29.1% of patients who discontinued romiplostim required TPO-RA re-initiation, pharmacologic therapy, or surgery. The most common reasons to re-initiate therapy were a decrease in platelet count and the presence of symptoms, such as clinically significant bleeding. The ITP experts also agreed that if the platelet count decreases or the patient develops clinically relevant symptoms, the treating hematologist, in conjunction with the patient, may need to re-evaluate tapering and, if necessary, revert to the previous TPO-RA dose.

ITP Expert Panel Opinion
- For patients who discontinue TPO-RA therapy, re-initiation of treatment may need to be considered if the platelet count decreases or the patient develops clinically relevant symptoms.

Discussion

In patients with ITP who show an adequate response to TPO-RA treatment, there is some evidence to suggest that TPO-RA therapy may be tapered with the intent of discontinuation, with monitoring to re-initiate therapy when platelet levels decrease beyond a certain threshold [17, 20, 28]. The results from our survey suggest that at least a subset of UK hematologists have applied such a tapering and discontinuation strategy in their patients with ITP (35 and 47% of those treated with eltrombopag or romiplostim, respectively). Despite the absence of broader guidelines, there appears to be a willingness among the responding physicians to try a tapering and discontinuation strategy in suitable patients. Our findings align with a previous review of practice among UK hematologists, which showed that most hematologists would taper down TPO-RAs in patients with stable platelet counts, although the definition of a stable platelet count varied among respondents [29].

In the absence of published guidelines, our panel of ITP experts achieved consensus regarding initial practice strategies related to potential tapering and discontinuation of TPO-RA therapy. The consensus was that tapering and discontinuation may be considered after 6–12 months of TPO-RA treatment for patients with an adequate treatment response (defined as a platelet count >50,000/μL in at least 75% of assessments in the preceding 6 months, i.e., a stable platelet count). Our findings are consistent with published reports on TPO-RA discontinuation and support this approach for select patients with ITP.

Potential benefits of intermittent versus continuous therapy include improved convenience that could enhance patient compliance and treatment satisfaction since patients may prefer treatments that can be given intermittently or even discontinued [21]. Long-term use of TPO-RAs is associated with tolerability issues, which have not yet been fully elucidated. For example, the significance of increased bone marrow fibrosis remains uncertain [30]. Furthermore, discontinuing TPO-RA therapy in patients with stable disease may reduce treatment costs, use of resources, and patient and physician burden.

Numerous approaches to tapering and discontinuation with varying results have been reported [10, 17, 19, 20, 22, 23, 28]. Most were small, retrospective studies based on case series from a single centre. Platelet counts achieved with TPO-RAs before tapering or discontinuation ranged between 50,000 and 150,000/μL in some studies [17, 22] but were much higher (>850,000/μL in individual patients) in most studies [10, 17, 19–23]. In clinical trials, more than 80% of patients with ITP respond to eltrombopag (response defined as platelet count ≥50,000/μL) [5], and response was maintained with long-term treatment (31 weeks) in >50% of cases [6]. One prospective study has been reported in which romiplostim was systematically tapered in patients with ITP who achieved platelet counts ≥50,000/μL within 1 year [31]. Almost one-third of patients (*n* = 24/75) maintained stable platelet counts ≥50,000/μL for >24 weeks. In the REPEAT study, 32 patients treated with eltrombopag ≤75 mg/day for ≥4 months and platelet count >50,000/μL were tapered at 4-week intervals in 10–20% dose increments over 2 years [28]. This study showed that intermittent short-term eltrombopag may be an ef-

fective and safe alternative in patients with ITP who do not require daily therapy but who do require intermittent use.

Our panel participants reported their patients to have treatment-free periods of approximately 2–3 months between discontinuing TPO-RA therapy and TPO-RA re-initiation, which was required in one-third of these patients. In previous studies, duration of TPO-RA treatment before tapering or discontinuation typically ranged between 6 and 12 months (range, 0.07–70 months) [10, 17, 19, 20, 22, 23]. In studies with a median follow-up of 6–12 months or more, sustained off-treatment response after discontinuation of eltrombopag or romiplostim was seen in 5–30% of patients [10, 18–23]. Relapses were observed in 8–47% of patients after discontinuation [19, 20, 22]. Few patients required rescue therapy during follow-up [10, 17–22]. For example, in a Spanish registry study, 11 of 12 patients responded to re-treatment with TPO-RAs [19]. Real-world data showed similar results: 53–64% of US patients with ITP discontinued eltrombopag, mostly within 6 months after treatment initiation [24]. Approximately 25% of these patients restarted eltrombopag; of those who did not, 16.7–55.6% did not receive any other treatment for ITP.

In the survey, hematologists reported a decrease in platelet count to be the primary driver of their decision to re-initiate treatment after a TPO-RA treatment-free period. These reports suggest that physicians do not always wait until clinical symptoms manifest and highlight the importance of continued monitoring of laboratory values after TPO-RA discontinuation. Our findings are in line with a previous review of practice among UK hematologists, which showed that most hematologists would taper down TPO-RAs in patients with stable platelet counts, although the threshold platelet count that would trigger a treatment taper ranged from 50,000 to 150,000/μL [29].

The ITP expert panel reinforced the absence of explicit, proven methods to predict patient suitability for a TPO-RA tapering and discontinuation strategy. Available evidence suggests that patient age, disease duration, and treatment history do not reliably predict sustained off-treatment response after TPO-RA discontinuation [17, 18, 22, 23]. Červinek and colleagues [17] suggested that the TPO-RA dose needed to achieve a response may serve as a possible predictive marker. However, these preliminary results are based on small studies that were insufficiently powered to identify predictive factors. In one prospective trial [22], lower absolute immature platelet fraction value at discontinuation predicted sustained re-

sponse. The other prospective study identified did not corroborate these findings [18].

Another remaining unmet need is the lack of standardized definitions for "successful off-treatment response" and "sustained off-treatment response." In some studies, these definitions were left to the treating physician's discretion or were not reported at all, possibly since platelet counts are specific to the individual. In 2009, an international working group defined complete response as platelet count ≥100,000/μL and absence of bleeding, whereas response was defined as a platelet count ≥30,000/μL and at least a twofold increase in the baseline count and absence of bleeding [25]. Successful or sustained off-treatment response was not defined by the international working group. Efforts should be undertaken to standardize these definitions.

Conclusions

This study confirms that TPO-RAs may be discontinued successfully in some patients with ITP. In the absence of established guidelines, our ITP expert panel reached consensus that hematologists may consider TPO-RA tapering and discontinuation after 6–12 months for patients with an adequate treatment response (platelet count >50,000/μL in at least 75% of assessments in the preceding 6 months). Long-term prospective studies are warranted to determine whether this approach is indeed optimal, and predictive markers are needed to identify patients with ITP who may successfully stop TPO-RA treatment.

Statement of Ethics

The paper is exempt from Ethics Committee approval since no patients participated in the study. All the participants have given their consent for being a part of the study. The authors have no ethical disclosures to declare.

Conflict of Interest Statement

Funding Sources

Author Contributions

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