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2022 Review of the 2019 American Society of Hematology Guidelines on Immune Thrombocytopenia

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Abstract:
The 2019 ASH guidelines for immune thrombocytopenia (ITP) included recommendations on management of adults (recommendations 1-9) and children (recommendations 10-21) with primary ITP (1). We describe here results of a review of the 2019 guidelines by a working group of experts requested by ASH to inform decision-making about the need for and timing of a guideline revision. An updated Medline and Embase search applied the same search terms as in the 2019 ASH guidelines, limited to systematic reviews and clinical trials, from May 2017 to July 2022. There were 193 studies identified, 102 underwent abstract review and 54 full review. Each study was assessed based on relevance to the previous recommendation with regards to the population, prioritized outcomes, new outcomes, and study design. Reviewers assessed if the data would change the strength or the directionality of the existing recommendation or merit development of a new recommendation. Based on this review, the ASH Committee on Quality endorsed a focused update on second-line management for adults with ITP. In addition, there will be continued annual monitoring and reviewing of the 2019 ASH guidelines on ITP in full to evaluate when there is sufficient new evidence to warrant additional revisions.

Conflict of interest: COI declared - see note

COI notes: C.N: Research Funding- Novartis; Consultant - Novartis, Argenx, and Sanofi; Educational Funding - Sobi; Royalties - UpToDate; Medical Advisor: UK ITP Support Association and ITP Australia (unpaid) D.A: Research Funding - Novartis and Rigel; Consultant - Novartis, Rigel, Amgen, Medison, Daiichi Sankyo, Sobi, Chugai, Principia, Takeda, Cellphire, Alpine, Argenx and Sanofi; Royalties - UpToDate; Medical Advisor: Platelet Disorders Support Association (unpaid) R.G: Research Funding- Novartis, Sobi, and Agios; Advisory Board - Agios and Sanofi; Medical Advisor: Platelet Disorders Support Association (unpaid) T.K: Research Funding - Amgen and Novartis; Advisory Board - Argenx, Sobi, and UCB K.M: Data Safety Board - Argenex; Advisory Board - Novartis and Alpine Bioscience D.T: Advisory Board - Sanofi

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Title: 2022 Review of the 2019 American Society of Hematology Guidelines on Immune Thrombocytopenia

Short running title: Update of the 2019 ASH Guidelines on ITP

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Abstract

The 2019 ASH guidelines for immune thrombocytopenia (ITP) included recommendations on management of adults (recommendations 1-9) and children (recommendations 10-21) with primary ITP (1). We describe here results of a review of the 2019 guidelines by a working group of experts requested by ASH to inform decision-making about the need for and timing of a guideline revision. An updated Medline and Embase search applied the same search terms as in the 2019 ASH guidelines, limited to systematic reviews and clinical trials, from May 2017 to July 2022. There were 193 studies identified, 102 underwent abstract review and 54 full review. Each study was assessed based on relevance to the previous recommendation with regards to the population, prioritized outcomes, new outcomes, and study design. Reviewers assessed if the data would change the strength or the directionality of the existing recommendation or merit development of a new recommendation. Based on this review, the ASH Committee on Quality endorsed a focused update on second-line management for adults with ITP. In addition, there will be continued annual monitoring and reviewing of the 2019 ASH guidelines on ITP in full to evaluate when there is sufficient new evidence to warrant additional revisions.

Introduction

The 2019 ASH guidelines for immune thrombocytopenia (ITP) included recommendations on management of adults (recommendations 1-9) and children (recommendations 10-21) with primary ITP (1). The guidelines addressed treatment of newly diagnosed ITP as well as persistent and chronic ITP with regards to hospitalization, observation, and treatment selection of both first and second-line agents. The guidelines also carried forward recommendations from the 2011 ASH guidelines for ITP related to diagnostic testing in patients with ITP, management of *H.pylori*, hepatitis C, human immunodeficiency virus, and measles mumps rubella vaccine associated ITP (2). This review of the 2019 guidelines by a working group of experts was requested by ASH to inform decision-making about the need for and timing of a guideline revision.

Literature Review Methods

ASH contracted with the University of Oklahoma Health Sciences Center (OUHSC) to refresh the literature searches conducted for the 2019 guidelines. Project oversight was provided by the ASH Guideline Oversight Subcommittee. D.T. vetted and retained researchers to conduct the updated search. The updated Medline and Embase search applied the same search terms as in the 2019 ASH guidelines. The search was limited to systematic reviews and clinical trials from May 2017 to July 2022. Non- English language and duplicates were removed. Identified studies (n= 193) were screened by title by one reviewer (C.N.) for relevance to the scope of the guidelines. Studies deemed out of the scope were reviewed by title by all reviewers (C.N., D.A., R.G., T.K., K.M.) and excluded. The remaining 102 studies underwent abstract review by 2 reviewers for number of patients, study design, and relevance. Reviewers ranked studies 1-3 (1 include, 2 possibly include, 3 exclude) and the average score between the 2 reviewers

was calculated. Studies with an average score of 1 were included and those with a score of 3 were excluded. The remaining studies were discussed by the entire group and were included or excluded by consensus. Studies selected for full review (n=54) were grouped by their relevance to an existing guideline recommendation (both 2011 and 2019) or the need for a new recommendation (Table 1) and reviewed by 2 reviewers. Each study was assessed based on relevance to the previous recommendation with regards to the population, prioritized outcomes, new outcomes, and study design. Reviewers assessed if the data would change the strength or the directionality of the existing recommendation or merit development of a new recommendation.

Relevant findings

The primary findings related to updating the guideline are highlighted below. Table 1 outlines all areas where articles were identified, and revisions were considered.

Adults with newly diagnosed ITP

Corticosteroids remain the backbone of therapy for ITP. The 2019 guidelines suggest either prednisone (0.5-2.0/mg/kg/day) or dexamethasone (40mg/day for 4 days) as the type of corticosteroid for initial therapy in adults with newly diagnosed ITP (Recommendation 4). Two new systematic reviews and 1 randomized trial were identified (3-5). The systematic reviews included one study not considered in the original 2019 guidelines and 2 non-English studies that were excluded. Inclusion of this paper did not change the strength or direction of the current recommendation. A randomized trial favored 3 courses of dexamethasone over prednisone for newly diagnosed and treatment naïve patients based on higher sustained remission (4). Due to the heterogeneity of the population, need for three courses of dexamethasone, no difference in additional outcomes and < 50 patients per study arm, this study was not felt to change the current recommendation.

The 2019 guidelines suggest corticosteroids alone rather than rituximab and corticosteroids for initial therapy (Recommendation 5). There were no new trials that addressed this recommendation. However, trials of combination therapy with corticosteroids and recombinant human thrombopoietin receptor agonists (TPO-RAs), all-trans retinoic acid, and mycophenolate mofetil were identified (6-8). We acknowledged that the landscape of upfront management is evolving, however given the heterogeneity of the studies, did not feel that there was sufficient data to require a new recommendation. Trials in upfront combination therapy should be assessed with an emphasis on cost, patient-related outcomes, and shared-decision making.

Children with newly diagnosed ITP

The 2019 guidelines recommend observation rather than intravenous immunoglobulin (IVIg) in children with newly diagnosed ITP and who have no or minor bleeding (Recommendation 12). The guidelines commented on the randomized trial of IVIg versus observation that was published after the original search (9). The trial included 200 children with newly diagnosed ITP randomized to either IVIg or observation alone. The authors found no difference in the guideline prioritized outcome of chronic disease.

Higher rates of bleeding were seen in the observation arm, however the population included children with moderate bleeding; therefore, the results do not directly apply to the patient population in this recommendation. Bleeding was not increased in children with no or mild bleeding at diagnosis treated with observation, the population included in the guideline and therefore, this trial supports the certainty of the current recommendation.

Adults with persistent and chronic ITP who are corticosteroid dependent or have no response to corticosteroids

The 2019 guidelines suggest a TPO-RA rather than rituximab and suggest either a TPO-RA or splenectomy for adults with persistent and chronic ITP lasting $\geq$ 3 months who are corticosteroid dependent or have no response to corticosteroids (Recommendations 7 and 9 respectively). TPO-RAs included in the 2019 guidelines included romiplostim and eltrombopag. The guidelines suggested either romiplostim or eltrombopag (Recommendation 6) and commented on the recent FDA approval of avatrombopag. Approval of avatrombopag provides a third agent when considering use of a TPO-RA and any updates to the guidelines would need to consider all available TPO-RAs, including hetrombopag available in China, however there were no substantial differences amongst the newer TPO-RAs that would change the recommendations regarding TPO-RAs as a drug class. We further acknowledged that the paired comparisons of TPO-RAs, rituximab and splenectomy led to discordant recommendations and that alternate strategies for formulating recommendations with multiple comparators may be preferrable.

The 2019 guidelines commented on the syk inhibitor fostamatinib. All clinical trials, however, were published after the conclusion of the original search. The updated search identified 3 studies on the use of fostamatinib (10-12). These studies had the same limitations recognized in the 2019 guideline in that the drug was mostly investigated in highly refractory patients failing multiple agents, therefore its role in this population is less clear. The group acknowledged that fostamatinib received an FDA indication for patients with chronic ITP who had an insufficient response to a previous treatment. We also recognized the emergence of new data in support of fostamatinib since the publication of the original guideline.

Children with ITP who have non–life-threatening mucosal bleeding and/or diminished Health Related Quality of Life (HRQoL) and do not respond to first-line treatment

The 2019 guidelines suggest TPO-RAs rather than rituximab or splenectomy in children who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment (Recommendations 19-21). Trials of sirolimus, cyclosporine, and hydroxychloroquine have been published since the 2019 guideline, however the size of the trials does not merit updated recommendations (13, 14).

Conclusions

The 2019 ASH guidelines on the management of ITP continue to be relevant and important, including recommendations related to second-line therapy for adults. We conclude that there is insufficient evidence to justify a revision of the entire guideline at

this time. We also recognize, however that the 2019 recommendations on second-line therapy for adults were the result of paired comparisons of splenectomy, rituximab and the TPO-RAs, and were based on a heterogeneous patient population. This resulted in discordant recommendations. Therefore, we recommend that a focused revision on second-line therapy for adults be conducted. We appreciate, that due to the absence of comparative randomized trials and the lack of reporting on prioritized patient-related outcomes, recommendations on second-line therapy will likely remain highly dependent on patient values and preferences even with additional clinical trials. Preference for agents may also change with prioritization of different outcomes and clinical contexts, such as the desire to avoid immunosuppression in the era of COVID-19. The updated search conducted here also identified alternate methodological approaches that would allow comparisons across several treatment strategies (15, 16). GRADE also outlines methodology for multiple comparisons that applies the evidence to decision framework (17). Use of these methods and refinement of the population of interest may clarify the existing recommendations. This would also provide the opportunity to be inclusive of avatrombopag and fostamatinib, discussed above, as well as novel agents currently in clinical trial development (18-20). Based on this review, the ASH Committee on Quality endorsed a focused update on second-line management for adults with ITP. This update will involve selection of a guideline panel, determination of appropriate questions, conduct of relevant literature searches, application of GRADE methodology, and publication of final recommendations. In addition, there will be continued annual monitoring and reviewing of the 2019 ASH guidelines on ITP in full to evaluate when there is sufficient new evidence to warrant additional revisions.

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Author Contributions:
D.T conducted the literature search. C.N, D.A, R.G, T.K, K.M conducted the systematic review of the identified literature. C.N wrote the first draft of the manuscript and all authors contributed to revising and finalizing the manuscript.

Conflicts of Interest:
C.N: Research Funding- Novartis; Consultant – Novartis, Argenx and Sanofi; Educational Funding – Sobi; Royalties - UpToDate; Medical Advisor: UK ITP Support Association and ITP Australia (unpaid)
D.A: Research Funding – Novartis and Rigel; Consultant – Novartis, Rigel, Amgen, Medison, Daiichi Sankyo, Sobi, Chugai, Principia, Takeda, Cellphire, Alpine, Argenx and Sanofi; Royalties - UpToDate; Medical Advisor: Platelet Disorders Support Association (unpaid)
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K.M: Data Safety Board – Argenex; Advisory Board – Novartis and Alpine Bioscience

D.T: Advisory Board - Sanofi

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Figure 1: Literature search results

Table 1: Summary of primary systematic review findings

Subject	Update or New Recommendation	Previous Recommendation	Number of studies	Comments
Adults with Newly Diagnosed ITP				
Prednisone or dexamethasone	Update	2019 Recommendation 4	3	
H. pylori eradication	Update	2011 Recommendations 7.3.A and 7.3.B	2	
IVIg	Update	2011 Recommendation 4.3A	2	
Combination Therapy	New		3	Agents used in combination with steroids: All-trans retinoic acid Mycophenolate Mofetil rhTPO
Children with Newly Diagnosed ITP				
Observation or IVIg	Update	2019 Recommendation 12	3	
Prednisone or dexamethasone	Update	2019 Recommendation 15	1	
Anti-D immunoglobulin or IVIg	Update	2019 Recommendation 17	2	
IVIg with or without IV methylprednisolone	New		1	
Adults with ITP for ≥ 3 months who are corticosteroid dependent or failed corticosteroids				
TPO-RAs (avatrombopag, eltrombopag, hetrombopag and romiplostim)	Update	2019 Recommendations 7 and 9	17	
Low dose Rituximab	Update	2019 Recommendations	1	

		8 and 9		
Splenectomy	Update	2019 Recommendations 7 and 8	1	
Fostamatinib	New		3	
Rituximab with or without cyclophosphamide	New		1	
Rituximab with or without all-trans retinoic acid	New		1	
Danazol with or without all-trans retinoic acid	New		1	
Hydroxychloroquine	New		1	
IVIg or eltrombopag for surgery	New		1	
Children with ITP who have non-threatening mucosal bleeding and/or diminished quality of life and do not respond to first-line treatment				
TPO-RAs (eltrombopag and romiplostim)	Update	2019 Recommendations 19 and 20	3	1 included in both adult and peds
TPO-RAs and Rituximab	Update	Recommendation 19	1	
Splenectomy	Update	2019 Recommendations 20 and 21	1	Included in both adult and peds
Sirolimus versus cyclosporine	New		1	
Hydroxychloroquine	New		1	
Multiple Comparison Studies				
Comparative Effectiveness in children with ITP			1	
Network Meta-Analysis in adults with ITP			2	
Multiple agents single center experience			1	

Figure 1: Literature search results