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Strategies for the prevention and management of Methotrexate-related nausea and vomiting in Juvenile Idiopathic Arthritis: results of a UK Paediatric Rheumatology prescriber survey.

Amin, T; Shenton, S; Mulligan, K; Wedderburn, LR; Wood, M; VanRooyen, V; Leone, V. *Rheumatology*, 2015

Methotrexate (MTX) is the most commonly used disease modifying anti rheumatic drug (DMARD) in the management of juvenile idiopathic arthritis (JIA). Gastrointestinal (GI) side effects include anticipatory, associative and post MTX nausea and vomiting (N&V) and using patient and parent reported data, are seen in at least 50% of patients taking MTX for JIA [1,2]

These side effects often limit the use of MTX, have a significant impact on quality of life [2, 3] and can be a reason to escalate to second line treatment with a biologic agent, which has significant health economic implications.

In UK paediatric rheumatology practice, variable strategies are used to prevent and manage MTX related N&V. In contrast to evidence-based guidelines available for emetogenic drugs in Paediatric oncology [4], no completed research studies or national guidelines on the use of antiemetics or other strategies to prevent and manage MTX-related N&V in JIA have been published. A PubMed search for evidence on the prevention and management of nausea and vomiting in non oncological use of methotrexate was performed and is presented in Supplementary information Table 1. This showed that evidence for the use of antiemetics or other strategies in conditions similarly treated with MTX in either adults or children, such as rheumatoid arthritis or Crohn disease, is very limited [5-8]

We aimed to identify the strategies currently in use amongst prescribing members of the British Society of Paediatric and Adolescent Rheumatology (BSPAR) for the prevention and treatment of MTX related N&V, with a view to informing future prospective studies. BSPAR is a national organisation whose members are practicing doctors, nurses, allied health professionals and researchers within Paediatric Rheumatology from across the UK.

An online survey using Survey Monkey web based software was devised and an invitation with weblink was circulated to the entire BSPAR membership, currently including an estimated number of 136 prescribers of MTX for JIA. A subsequent reminder was sent out 2 months later. A summary of the main questions asked and results of responses is shown in Supplementary Table S1, available at *Rheumatology* online.

Eighty-four respondents completed the survey including 29 of 45 practising UK Paediatric Rheumatology consultants, 22 Paediatricians and 10 Consultant Adult Rheumatologists with an interest in Paediatric Rheumatology, and 21 other prescribing practitioners with a 62% overall response rate.

Over half of all respondents estimated that N&V developed in >25% of JIA patients on MTX and 63% of respondents estimated that greater than 10% of patients were changed to biologic agents primarily due to gastrointestinal side effects.

On starting methotrexate for the treatment of arthritis in JIA, only 21% of respondents always or often (defined as greater than 50% of the time) start an antiemetic. Ondansetron was the first choice of antiemetic for 88% of respondents. Factors increasing the likelihood of prescribing antiemetic drugs were a child prone to nausea and vomiting and parental anxiety or request.

In relation to concomitant folic acid, 67% of respondents always or often start folic acid. No other strategy to prevent side effects was routinely used.

The three most common strategies to deal with anticipatory N&V related to MTX, combining first and second choices (when not routine on starting MTX) were: starting an antiemetic (70%), a team member teaching behavioural techniques (49%) and changing the route of administration of MTX (38%). Clinical psychology and adding folic acid were used with a similar frequency (37%).

The most frequently used management strategies for post-MTX N&V, combining first and second choices (when these were not routine on starting MTX) were: starting an antiemetic (100%), starting folic acid (74%) and changing the route of administration of MTX (57%).

Clinical psychology intervention was used within the first 3 strategies by 73% and 35% of respondents for anticipatory N&V and post MTX N&V respectively. However access to care may have limited the use of this strategy with 22% of respondents reporting no access at all to clinical psychology services and only 30% of respondents benefitting from a dedicated service. Changing to a biologic was considered by 57% and 54% of respondents, as third choice or lower strategy for managing anticipatory or post MTX- related nausea. However only 5 % of respondents stated they would not consider this strategy for MTX related side effects. In summary MTX-related N&V is recognised as a common problem amongst prescribers of MTX for JIA potentially significantly contributing to the need to escalate treatment to biologic drugs. Preventative approaches and in particular antiemetic prescribing on starting MTX to prevent anticipatory and post-MTX N&V, are not supported by evidence of efficacy and are inconsistently used. Variable strategies are used to manage side effects, including the use of anti-emetics, folic acid and psychological interventions.

This survey identified the most commonly used strategies used by a significant proportion of UK MTX-prescribers for JIA. A study to compare these strategies, including the preventative use of antiemetics, is urgently needed and strongly supported by the MCRN/Arthritis Research UK Clinical Study Group including the consumer representatives.

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Supplementary Information

Table 1 Summary of PubMed searches for studies into the prevention and management of Methotrexate related nausea and vomiting (non-oncological use).

Search Terms	Number of papers returned	Number of relevant papers	References	Summary of findings
Methotrexate	123	2	Blanco R, Gonzalez-Gay MA,	<i>Open label interventional</i>

AND Antiemetic AND Arthritis			<p>Garcia-Porrúa C, et al. Ondansetron prevents refractory and severe methotrexate-induced nausea in rheumatoid arthritis. <i>Br J Rheumatol.</i> 1998; 37:590–591 [6].</p> <p>Devlin J, Wagstaff K, Arthur V, et al. Granisetron (Kytril) suppresses methotrexate induced nausea and vomiting among patients with inflammatory arthritis and is superior to prochlorperazine (Stemetil). <i>Rheumatology.</i> 1999;38: 280–82 [7].</p>	<p><i>study.</i> 9 adult patients with RA and nausea refractory to metoclopramide and switch to IM route. All patients had reduction in nausea duration and intensity with ondansetron.</p> <p><i>Randomised single blinded interventional study.</i> Comparison of granisetron vs prochlorperazine in 13 adult patients with RA or Psoriatic Arthritis. All patients randomised to granisetron reported significantly improved symptoms compared to those randomised to prochlorperazine.</p>
Methotrexate AND Prevention AND Nausea	60	2	<p>Kempinska A, Benchimol EI, Mack A, et al. Short-course ondansetron for the prevention of methotrexate-induced nausea in children with Crohn disease. <i>J Pediatr Gastroenterol Nutr.</i> 2011 Oct;53(4):389-93 [8].</p> <p>Shea B, Swinden MV, Tanjong Ghogomu E, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. <i>Cochrane Databases</i></p>	<p><i>Retrospective case control study.</i> 64 children with Crohn disease on methotrexate. 4 of 50 patients given ondansetron on starting methotrexate developed nausea vs 6/10 patients not prescribed ondansetron.</p> <p><i>Meta-analysis of 6 RCTs of low dose folic or folinic acid supplementation with MTX including 624 patients with RA.</i> 26% relative risk reduction of the incidence of GI side effects.</p>
Methotrexate AND Treatment AND Nausea	756	2 (excluding previously reported papers)	<p>van der Meer A, Wulffraat NM, Prakken BJ, Gijsbers B, Rademaker CM, Sinnema G. Psychological side effects of MTX treatment in juvenile idiopathic arthritis: a pilot study. <i>Clin Exp Rheumatol.</i> 2007 May-Jun;25(3):480-5 [10].</p> <p>Alsufyani K, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Malleson PN. The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. <i>J Rheumatol.</i> 2004 Jan;31(1):179-82 (not</p>	<p><i>Case series</i> of 29 patients with JIA on MTX. 10 were referred to psychology for MTX side effects with improvement in symptoms.</p> <p><i>Retrospective case series</i> of 61 children with JIA, 31 of whom switched to SC MTX for oral MTX inefficacy or side effects. 9 of 11 children with nausea reported improvement after change of route.</p>

		reference in the main paper).	
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Abstracts were reviewed by the main author and prospective and retrospective observational and interventional studies regarding the use of antiemetics and other strategies to prevent nausea and vomiting in non-oncological regimens using methotrexate were included. Single case reports were disregarded.

Several papers related to the use of folic and folinic acid have been omitted due to their inclusion in the Cochrane systematic review on this subject.