Letter of response

Date 29 October 2022

To the WHO EML secretariat,

We are writing in response to the WHO EML committee's request for additional information with respect to our 2021 applications for anakinra (IL-1 inhibitor), tocilizumab (IL-6 inhibitor) and triamcinolone hexacetonide to be added to the complementary list in the EML, EMLc and eEMLc-section 'Joint Diseases in Children'.

The World Health Organisation (WHO) Essential Medicines List (EML) informs countries about the minimum medicine items necessary to meet priority health needs and guides national and institutional medicine lists, especially in low and middle income countries. Aligning the medicines in the WHO EML with current best clinical practice enables appropriate evidence-based prescribing, easier access, improved affordability of medicines and consequently, improved outcomes.

The Paediatric Global Musculoskeletal Task Force (TF) worked to identify the most essential medicines to be added to the WHO EML for rheumatic diseases in children[1] and submitted applications for the addition of anakinra (IL-1 inhibitor), tocilizumab (IL-6 inhibitor) and triamcinolone hexacetonide in 2021.

In response to feedback from the EML committee for more information about the use of these medicines in clinical practice, we submit a narrative review which focuses on juvenile idiopathic arthritis (JIA) and current management approaches of this group of heterogeneous rheumatic disorders. The TF also conducted a global survey to identify the medicines needed in the WHO EML for the treatment of JIA and the challenges to their use.[2] Importantly, as highlighted in our review and survey, the medicines already listed in the WHO EML (methotrexate, tumour necrosis factor inhibitors and chloroquine), do not reflect standards of care for JIA.

Further, strongly supported by the survey results, lack of access and affordability of medicines were deemed major barriers to providing care for children with JIA and anakinra (IL-1 inhibitor), tocilizumab (IL-6 inhibitor) and triamcinolone hexacetonide (intra-articular corticosteroid), were identified as medicines that 'must be included in the WHO EML'.[2]

The addition of these medicines, substantiated by current best clinical practice guidelines (as outlined in our review), and by consensus from our surveys, will provide an appropriate portfolio of medicines to address the treatment approaches needed to manage the heterogeneity in JIA.

We thank the EML committee for the opportunity to respond to several specific questions regarding the additions to the complementary list in the EML, EMLc and eEMLc- section 'Joint Diseases in Children' of:

- Anakinra for the treatment of systemic onset juvenile idiopathic arthritis (SOJIA) with macrophage activation syndrome (MAS)
- Tocilizumab for the treatment of SOJIA without MAS
- Triamcinolone hexacetonide for intra-articular injections

To **the** ***request for a comprehensive overview of the medicines used in the management of juvenile idiopathic arthritis,*** we provide an up-to-date narrative review, with the rationale for current treatment strategies (Appendix 2). Key advancements in scientific knowledge and subsequent changes in the recommended evidence-based guidelines contributing to the modern management of JIA are highlighted.

The committee also requested clarity on treatment guidelines for SOJIA, specifically questioning the benefit of adding tocilizumab to the EML for JIA, when alternative medicines such as TNFi are already listed, and are described in current treatment guidelines.

The review (Section 3.1) discusses the cytokines involved in the pathogenesis of SOJIA (as it is currently understood), explains the heterogeneity in the clinical phenotypes of SOJIA, and the role

of specific cytokine inhibitors in treatment. The review acknowledges the difficulties in treating SOJIA and reports treatment options in view of this.

SOJIA, a polygenic autoinflammatory disease unlike the other JIA subtypes, is mediated by the IL-1 family of cytokines. IL-1 and IL-6 inhibitors are potentially lifesaving when used in the 'treatment window of opportunity' and are therefore advocated to limit the adverse effects of long-term corticosteroid use and to improve outcomes.

Randomised controlled clinical trials (Table 1) supported by longer term open label studies (Table 2), show efficacy for both IL-1 and IL-6 inhibitors in the treatment of SOJIA.[3–6] Meta-analyses of the bDMARDs used in the treatment of SOJIA (reported by indirect analyses), showed no difference in efficacy between IL-1 inhibitors and tocilizumab for the treatment of SOJIA and although all were superior to placebo, (Fig. 1) canakinumab and tocilizumab were more effective than rilonacept.[7]

The efficacy of tocilizumab in treating both systemic symptoms and arthritis has also been demonstrated. Tocilizumab is widely available and costs considerably less than the IL-1 inhibitors, where the cost of anakinra in this drug class is markedly less than canakinumab. (Tables 8 and 9 in the Review)

The committee further questioned the role of janus kinase (JAK) inhibitors as a treatment option in SOJIA

JAK inhibitors are potentially a new addition to the armamentarium for the treatment of JIA. JAK inhibitors have been approved for use in polyarticular JIA and a clinical trial in juvenile idiopathic arthritis associated uveitis is currently in the recruitment phase. Successful treatment of cases of refractory JIA associated uveitis have also been described. However, case reports and case series in refractory Still's disease, describe adult-onset disease and include very few children with SOJIA. Although results are promising, there are no clinical trials or data for longer term efficacy in SOJIA.[8–11] An application for JAK inhibitors will therefore not be submitted at this time, as there are insufficient data for its role in the treatment of SOJIA.

Addressing the question of the risks associated with treatment

Importantly, infection in children with JIA is significantly increased with doses of corticosteroid ≥10mg/day (adj.HR 3.1 [95% CI 2.0, 4.7]) independent of methotrexate or TNFi.[12,13]

An accurate assessment of the benefit-risk of bDMARDs is perhaps more difficult to ascertain. A meta-analysis of the RCT's in JIA for the benefit-risk of the bDMARDs used in JIA, reported that patients in the SOJIA category experienced therapeutic success with fewer SAEs when compared to the non-systemic category. The net benefit of anakinra could not be determined as no SAE's were reported.[14]

The adverse events ascribed to IL-1 and IL-6 inhibitors are well reported and appropriate monitoring for these are instituted accordingly before and during treatment as discussed in the review (Review Section 4). Infections such as tuberculosis represent an important risk in high prevalence countries and healthcare worker vigilance, specific screening protocols in addition to national guidelines, and patient education are advocated to enhance early detection, with a low threshold for treatment. Immunisations are also a routine part of the care of children with JIA.

The committee voiced concerns regarding the safety of triamcinolone hexacetonide intra-articular injections compared to oral corticosteroids or other DMARDs

Intra-articular corticosteroid injections (Review Section 3.2) provide rapid targeted effective relief of pain and swelling and are considered standard of care. The effect has been shown to last for up to 2 years, with the avoidance of systemic corticosteroids and without the addition of DMARDs in some cases. Should DMARDs be required, IAI bridges the time taken to reach steady state and exert a clinically appreciable effect. The addition of intra-articular corticosteroids to the WHO EML was deemed necessary by 91% of respondents and concern about procedure complications such as infections were reported by 10%.[2] Recent studies have reiterated the efficacy of intra-articular corticosteroids and the low rate of adverse events, which are usually mild injection site subcutaneous atrophy or fat necrosis and rarely iatrogenic infections (Review Section 4). The risk of Cushing's syndrome has also been reported as low - more soluble preparations and at higher doses than is currently recommended were used in the studies where Cushing's syndrome was reported, perhaps strengthening the case for triamcinolone hexacetonide.[15]

However, concerns should consider that the alternative medicine to intra-articular corticosteroids are systemic corticosteroids and as indicated, higher rates of infection have been shown in children with JIA using ≥10mg/day.

Challenges with access to specialist medical services in middle and low-income countries

The Task Force acknowledges the difficulties in providing care to children with JIA as discussed (Review Section 6).

A global perspective on these challenges in the 2022 TF survey noted that access, availability, and affordability of medicines were major barriers to care, despite the procedures of intra-articular injections, subcutaneous injections and intravenous injections being available most or all the time. The availability of trained personnel to perform the procedures were not deemed a major barrier by most, as patients or their parents/guardians generally administered the subcutaneous injections themselves after training (a useful indicator of the broader acceptability of these medicines).

While other factors were considered as limiting care, comments in these sections of the survey indicate awareness of these challenges and the ongoing work towards overcoming them.[2]

Amending the existing EML for joint diseases in children is an important step to enable appropriate treatment for children with JIA and will improve access, availability, and affordability of these medicines globally. This is particularly true in middle and low income countries where national formularies are often based on the WHO EML.

Given the significant role of intra-articular corticosteroids, anakinra and tocilizumab as noted in published clinical management guidelines and recommendations, and the evidence for efficacy and improved outcomes (as outlined in our report), as well as consensus derived from our survey; the TF deemed these to be the most appropriate medicines to propose for addition to the EML.

The TF updated applications for the medicines anakinra (IL-1 inhibitor), tocilizumab (IL-6 inhibitor) and triamcinolone hexacetonide to be added to the complementary list in the EML, EMLc and eEMLc- section 'Joint Diseases in Children' are submitted with the:

- Narrative review of the medicines used in the management of JIA, with the rationale for current treatment strategies to substantiate the applications
- The published 2022 TF survey reviewing medicines deemed to be important for the treatment of JIA, and the perceived challenges associated with their use
- Letters of support from the global rheumatology community

We appreciate the committee's willingness to review the applications and look forward to your reply.

Yours sincerely

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On behalf of the Paediatric Global Musculoskeletal Task Force

Table 1: Summary of RCT's SOJIA

Medicine	**Anakinra**	**Canakinumab**		**Rilonacept**		**Tocilizumab**	
Authors	**Quartier et al (2011)**[16]	**Ruperto et al (2012)**[17]	**Ruperto et al (2012)**[17]	**Lovell et al (2013)**[18]	**Ilowite et al (2014)**[19]	**De Benedetti et al (2012)**[20]	**Yokota et al (2008)**[21]
Study Type	pRCT	pRCT	wRCT	pRCT	pRCT	pRCT	wRCT
Population	2-20yrs	2-19yrs	2-19yrs	4-20yrs	≥ 18ms - 19yrs	2-17yrs	2-19yrs
Single/ Multi-centre	Multicentre	Multicentre	Multicentre	Multicentre	Multicentre	Multicentre	Multicentre
Comparator	placebo	placebo	withdrawal	placebo	placebo	placebo	withdrawal
Dose	2mg/kg	4mg/kg	4mg/kg	2.2mg/kg or 4.4mg/kg max 320mg	4.4mg/kg load max 320mg; 2.2mg/kg weekly maintenance max 160mg	≥30kg: 8mg/kg ≤ 30kg: 12mg/kg	8mg/kg
Time period in weeks	4	4	88	4	4	12	12
Effect Measure	ACR-pedi30 + absent fever and decrease CRP by 50% or normal CRP	ACR-pedi30 + absent fever	No JIA Flare	ACR-pedi30 +absent fever	ACR-pedi30 + absent fever and at least 10% tapering corticosteroids	ACR-pedi30+ absent fever	Maintain ACR-pedi 30+ CRP< 15mg/L

								*Time to response					
Arm **N**	ANA 12	PBO 12	CKB 43	PBO41	CKB 50	PBO 50	RLT 17	PBO 7	RLT 35	PBO 33	TCMB 75	PBO 37	TCMB 20	PBO 23
Primary outcome	8 (67%)	1 (8%)	36 (84%)	4 (10%)	39 (78%)	24 (48%)	6 (35%)	2 (29%)	26 (74%)	13 (39%)	64 (85%)	9 (24%)	16 (80%)	4 (17%)
p-value	p=0.003		p<0.001		p=0.003		Reported as no difference, no p-value		p=0.004		p<0.001		p<0.0001	
Odds ratio (95% CI)	NR		NR		NR		NR		4.54 (1.62;12.72)		NR		OR 19.00 (4.08, 88.38)	
†Risk difference (95% CI)	0.583(0.274;0.893)		0.74 (0.596; 0.883)		0.3 (0.120; 0.480)		0.067 (-0.337;0.472)		0.299 (0.075;0.522)		0.61 (0.45;0.77)		0.626 (0.392; 0.860)	
†NNT	2		2		4		15		4		2		2	

pRCT- parallel randomised controlled trials, wRC- withdrawal randomised controlled trials, ACR-Pedi – American College of Rheumatology paediatric Core set variable score indicating 30, 50, 70% improvement, PBO- placebo, ANA – anakinra, CKB – canakinumab, RLT – rilonacept, TCMB - tocilizumab

**The median time to response was 4 weeks (IQR 2;10) in the rilonacept group vs 8 weeks (IQR) in the placebo group p=0.007*

†Values calculated from summary data presented in studies

Comment

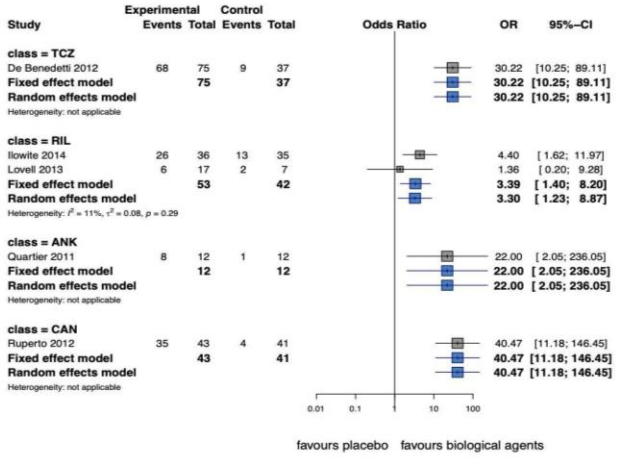
The differences in the randomised controlled trials design, small sample sizes, duration, endpoints, reporting methods and ethical considerations, highlights the difficulties of clinical trials in children. These trials continued with open label extension phases

Table 2: Summary of open-label extension phases

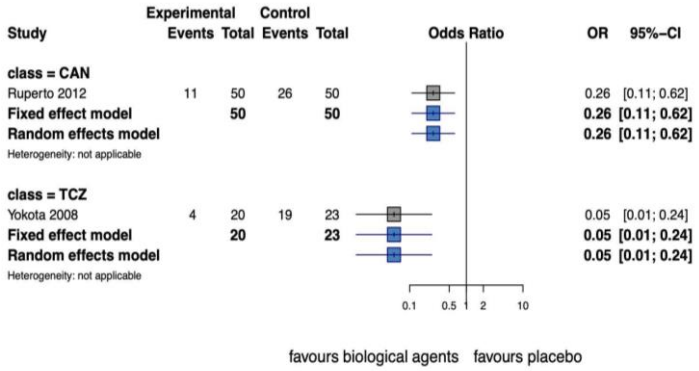
Open label extension phase						
Medicine	**Anakinra**	**Canakinumab**		**Rilonacept**		**Tocilizumab**	
Authors	Quartier et al (2011)[16]	Ruperto et al 2018[22]		Lovell et al (2013)[18]	Ilowite et al (2014)[19]	De Benedetti et al (2012)[20]	Yokota et al (2008)[21]
Effect Measure	ACR-pedi30 + absent fever and decrease CRP by 50% or normal CRP	ACR-pedi30 + absent fever	No JIA Flare	ACR-pedi50/70/90/100 +absent fever Safety	Time to response: ACR-pedi30 + absent fever and at least 10% tapering corticosteroids	ACR-pedi30+ absent fever	Maintain ACR-pedi 30+ CRP< 15mg/L
Period	11 months	60 months		24 months	15 months	12 months	11 months
N	22	144 - 75 completed, 102 discontinued mainly due to inefficacy		23	24	112	48
Outcome	Decreased prednisolone dose No SAE's reported	Response to canakinumab seemed to be sustained for early responders' group, glucocorticoid dose was reduced and discontinued in 33% MAS in 13 participants (7.3%) More frequent infections with canakinumab		Significant improvement in clinical and laboratory indicators of disease, including reduction in active joint count and corticosteroid use Overall rate of mild infection (69%), no TB or opportunistic infections	Significant reduction in corticosteroids No opportunistic infections Raised transaminases 1 episode of MAS triggered by EBV	Systemic and joint symptoms significantly improved. Continued improvement of active and limited joint count as well as childhood health assessment questionnaire, disability index	Tocilizumab is effective for SOJIA, sustained clinical improvement ↓ ESR, CRP from baseline 13 serious adverse events, mostly infection (no cases of TB) and one anaphylactoid reaction

Figure 1: Meta-analyses of biologics in SOJIA

(a) pRCT's



(b) withdrawal RCT's



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