Saving more lives from severe malaria

New evidence demonstrates the life-saving impact and feasibility of switching to injectable artesunate for the treatment of severe malaria

Around 5.6 million people fall prey to severe malaria every year, leading to an estimated 627 000 deaths, mostly of children under five years of age.[1] The results of two large-scale clinical studies, published in 2005 and 2010, demonstrated the clear superiority of injectable artesunate for the treatment of severe malaria over quinine, the previous standard of care. In Asia, a 34.7% reduction in mortality resulted when injectable artesunate was used instead of intravenous quinine in adults, while in African children, a comparable study showed a 22.4% reduction.[2,3] Based on this research, the World Health Organization (WHO) updated its standard treatment guidelines in 2011, recommending injectable artesunate as the preferred treatment for severe malaria. Médecins Sans Frontières (MSF) estimates that approximately 200 000 additional lives could be saved each year if malaria-endemic countries made the switch to injectable artesunate.[4]

Joining forces to make the switch

In response to this body of evidence, Medicines for Malaria Venture (MMV) joined forces with relevant stakeholders and partners to discuss the challenges relating to the treatment of severe malaria. The goal was to agree on a way forward to save more lives through increasing uptake and use of injectable artesunate across the malaria-endemic world. Representing 30% of the global population at risk, Nigeria and the Democratic Republic of the Congo (DRC) were identified as the two countries where the biggest impact could be made.

In July 2012, working with the National Malaria Control Programme (NMCP), key stakeholders and Clinton Health Access Initiative (CHAI), MMV set out to support six Nigerian states to make the switch. This involved raising awareness about the benefits of injectable artesunate, supporting a change to national guidelines, training healthcare workers, quantifying the need and monitoring the impact of the switch. Today, the drug is being procured with state funds in four of the six states.

In early 2013, the Programme National de Lutte Contre le Paludisme (PNLP) of the DRC adapted their policy with a new recommendation to use injectable artesunate as the preferred treatment for severe malaria. Making the switch, however, is a complex undertaking involving many operational and clinical adaptations. The strategic planning of the PNLP predicts that the percentage of patients present with severe malaria who receive injectable artesunate will increase from 30% in 2014 to almost all in 2016.

Based on the knowledge acquired in the DRC and Nigeria, MMV has established a severe malaria consortium with CHAI and the Malaria Consortium. In 2013, this MMV-led team was awarded a UNITAID grant of USD34 million to fund procurement and scale-up of injectable artesunate across 13 of the 36 states in Nigeria, and in five other high-burden African countries (Cameroon, Ethiopia, Kenya, Malawi and Uganda).

Up to 30-40 million vials of injectable artesunate would be needed worldwide each year to treat all estimated cases of severe malaria. Yet, currently, only 10 million vials are being manufactured annually. Owing to this shortfall and other constraints, an estimated 60-70% of severe malaria patients are left without access to the drug. The UNITAID project seeks to reduce this gap by stimulating greater market competition and eventually lowering prices for this important drug.

Focusing on safety

Following reports of haemolytic anaemia after treatment with injectable artesunate, in 2013, MMV convened a meeting to discuss the medicine's safety profile and make recommendations for its use.[5] Two key recommendations were made. First, physicians should be made aware of the need for continued monitoring of patients up to 28 days after treatment due to the possibility of delayed haemolysis after injectable artesunate administration. Second, further clinical trials need to be conducted in different patient populations to define the frequency and prognostic factors of haemolysis, and how to reduce them.

Later that year, WHO published a note building on these recommendations and concluding that there is overwhelming evidence that injectable artesunate is a generally well-tolerated and life-saving therapy, providing a significant reduction in mortality compared to quinine. The benefits of the medicine far outweigh the risks.[6]

To guide the optimal use of injectable artesunate as the scale-up proceeds, MMV is working with manufacturers to monitor the real-life safety of the medicine. For example, Guilin Pharmaceutical, who manufacture WHO prequalified injectable artesunate, has strengthened its pharmacovigilance activities to better assess the safety/tolerability of injectable artesunate in malaria-endemic countries.

> Since WHO prequalification in 2010, close to 12 million vials of Guilin's injectable artesunate have been delivered and are estimated to have saved between 80 000-90 000 additional lives compared to treatment with quinine.

Gathering evidence to support the switch

To gather the evidence to support the switch in the DRC and better understand the operational challenges, MMV, Swiss TPH and Kinshasa School of Public Health undertook the Malaria Treatment with Injectable Artesunate Study (MATIAS), which compared injectable

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artesunate treatment with quinine in four districts in and around Kinshasa.

The study consisted of two phases conducted sequentially at eight treatment centres, three hospitals and five health centres. In the first phase, 399 patients were recruited over a three-month baseline period and treated with intravenous quinine. Intravenous artesunate was then introduced for a following three-month period and 350 patients were treated. Consenting patients (if children via their parents) of two months of age or older with confirmed malaria were recruited. Four components were evaluated in each phase: 1) clinical assessment; 2) time and motion study;[7] 3) feasibility and acceptability assessment; 4) analysis of the financial costs.

Additionally, following reports of haemolytic anaemia after injectable artesunate administration, the protocol was adapted to include outcome and follow-up at days 14, 21, 28 after treatment, in addition to the already planned visit at day seven. The proportion of patients with severe anaemia in the study groups was below 1% for the whole duration of the follow-up period. In all cases, delayed anaemia was clinically manageable with appropriate and prompt care.[8] It should be noted that other studies have reported rates of delayed haemolysis in up to 7% of children treated with injectable artesunate.[9]

Overall, the respective case fatalities were 3.8% with quinine and 1.7% with artesunate, with a median time to discharge of three versus two days, respectively. The mean cost for treatment was 19-36 USD for quinine versus 17-28 USD for artesunate. Also, 75% of healthcare workers reported that artesunate was easier to use than quinine. The study therefore supports WHO recommendations for use of life-saving injectable artesunate for the treatment of severe malaria.[10]

The study findings provide compelling evidence about the feasibility of and positive health impact from introducing injectable artesunate in DRC, supporting its national deployment over three years through its inclusion into the country's 2013-2015 strategic plan.

Buying time for treatment

The first point of care for many patients with severe malaria is a community-level healthcare worker (CHW) or primary care facility. It is often not possible to deliver parenteral treatments at this level, and in such cases the WHO recommends the use of rectal artesunate suppositories (RAS)[11] as pre-referral treatment.

Thus, a WHO-prequalified RAS product is urgently needed to make treatment for severe disease available at this first point of care. This will buy time for them to seek services from higher-level (and better-resourced) health facilities with the capacity to provide the recommended treatment.

The aforementioned UNITAID grant is also being used to address this therapeutic gap. This process will build on clinical studies led by the WHO Special Programme for Research and Training in Tropical Diseases (WHO-TDR), which demonstrated the benefits of rectal artesunate.[12] MMV will support selected manufacturers of RAS to demonstrate bioequivalence between their products and the product used in WHO-TDR's studies, and subsequently seek WHO prequalification. Two such pharmaceutical partners have been identified and MMV is working with them to bring prequalified RAS to market by 2016.

In support of RAS rollout, MMV is conducting market research in 20 high-burden malaria countries to help optimise the use of the drug. The first step is to understand current guidance and practice regarding pre-referral treatment for severe malaria in priority countries. The next step will be to quantify the demand for rectal artesunate for 2016-2018 by the end of 2014 to help ensure that manufacturers can meet the need.

Conclusion

Today, we have a key tool to help save lives from severe malaria, injectable artesunate for treatment, and another one on the way, rectal artesunate for pre-referral treatment. MMV is working with partners to maximise the use of both. Already, tens of thousands of additional lives have been saved thanks to countries and healthcare workers making the switch from quinine to artesunate for treatment. Findings from the MATHIAS study have also demonstrated the feasibility of a switch. We know the impact this medicine can have and we know healthcare workers prefer to use it in place of quinine. Now is the time to work towards ensuring all severe malaria patients will receive this life-saving treatment. MMV will continue to work with partners to achieve this goal.

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