ImmunoStart: preparing patients for immunosuppression

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Abstract

Objectives: Patients with immune-mediated inflammatory disease (IMID) present an increased risk of infection. Here, we present the concept of a preventive consultation called ImmunoStart and the first results of its implementation in the care pathway of patients with IMID.

Methods: Relevant information about vaccination history, TB exposition and other infectious risks are collected through blood sampling, complete anamnesis, chest X-Ray and Mantoux test. During ImmunoStart consultation, vaccination schedules, specific treatments and risk considerations are discussed.

Results: Between October 2016 and February 2020, 437 patients were seen at the ImmunoStart consultation, mainly referred by rheumatologists (56%), dermatologists (25%), and gastroenterologists (18%). A total of 421 (96%) patients needed at least one vaccine (a mean of 3.3 vaccines per patient). Live attenuated vaccine was indicated for 45 patients (10%), requiring them to reduce or interrupt their immunosuppressive drug(s). Ninety-two patients (21%) were treated for latent TB infection.

Conclusion: This preventive consultation provides a centralized and systematic setting for the direct management of patients with IMID in need of vaccination, treatment of latent disease and specific advice regarding their immunomodulating treatments.
Keywords: IMID, prevention, immunosuppression, vaccination, screening, latent

Key messages:

- Screening and vaccinations in IMID patients should ideally take place before starting an immunomodulating treatment.
- A centralized setting allows all IMID patients to be systematically referred for this complete preventive management.
- A concept such as the ImmunoStart consultation makes it possible to carry out screenings and vaccinations under optimal conditions.
Introduction

Immune-mediated inflammatory diseases (IMID) are multifactorial systemic diseases with aberrant immune responses. Treatment is currently based on conventional synthetic disease modifying antirheumatic drugs (csDMARDS) and, in cases of treatment failure, on biological DMARDS (bDMARDS), biosimilar DMARDS (bsDMARDS) or targeted synthetic DMARDS (tsDMARDS). Patients with IMID bear an increased risk of infections due to the immunosuppressive effect of the underlying disease and the use of immunomodulatory medication to treat the IMID. Incidence as well as severity of infections are higher in patients with IMID, including incidence of vaccine-preventable infections (1)(2)(3)(4). In the last decade, many new b/bs/tsDMARDS have been developed for IMID patients, and an increasing number of indications are being recognized for their use. Moreover, they are used earlier in the course of IMID(5). International guidelines recommend screening for latent TB infection (LTBI) before TNF-α blocker prescription (6)(7). Guidelines for vaccination of patients with IMID (5)(8), including recent updated Belgian guidelines (9), are also available but several reports point out low adherence (10) (11). The main reasons for low adherence to vaccination are concerns about vaccine safety and lack of clarity about who is in charge of the patient's screening and vaccinations (10).

Methotrexate, corticosteroids but also abatacept, and some TNF-α blockers have shown deleterious effects on immune response after vaccination with inactivated vaccine, at least for primary vaccination (8)(12). Live attenuated vaccines (LAV) are contraindicated during immunosuppressive therapy due to the risk of disease from the live attenuated pathogen (12)(13). Finally, latent infections other than M. tuberculosis can also reactivate under specific immunomodulating treatments, such as occult hepatitis B (1) or shingles (Varicella Zoster.
virus reactivation). Therefore, there is a need for specific screening, for vaccinations and for targeted advice in patients with IMID, ideally before starting an immunomodulating treatment. Because it is challenging for IMID specialists to manage this “pre-therapeutic” assessment together with the disease therapy plan, a joint care program between IMID specialists (mainly gastroenterologists, rheumatologists, and dermatologists) and infectious disease specialists has been created in our hospital and called “ImmunoStart consultation”. ImmunoStart is led by a specialist in infectious diseases, with the aim to ensure a targeted screening, counseling, and vaccination program for each patient with IMID. This consultation is planned as soon as possible after IMID diagnosis. In this paper, we present the data from this innovative ImmunoStart consultation.

Materials and methods

The Centre Hospitalier Universitaire Saint-Pierre (CHU Saint-Pierre) in Brussels is a tertiary public hospital. Specialists in gastroenterology, rheumatology and dermatology of CHU Saint-Pierre created the “Biologic Platform”, an outpatient clinic welcoming about 200 new patients with IMID per year. Patients are prospectively followed-up, treated with standard of care and/or enrolled in therapeutic clinical trials and their data are centralized in a database after having signed an informed consent. All adult patients (primarily new patients) are referred to the ImmunoStart consultation as soon as possible even if they are already treated with an immunomodulating drug. Patients with a flare-up of their disease or patients who already performed a vaccinal work up and were already screened for LTBI are not (immediately) addressed to the consultation. Following serological analysis are performed before the ImmunoStart consultation: hepatitis A, B and C, Treponema pallidum, Measles, Rubella (women only), Varicella, HIV, sometimes Trypanosoma cruzi and Strongyloides stercoralis if
the patient originates from an endemic area. Interferon Gamma Release Assay (IGRA) is performed. If HBsAg or HBcAb (without HBsAb) is positive, hepatitis B virus DNA is measured. Chest X-Ray (+/- chest Computerized Tomography if X-Ray is abnormal) and Mantoux test are performed before the ImmunoStart consultation.

During the ImmunoStart consultation, medical history, former and current treatment, country of birth, travel history and plans, immunization history, tuberculosis contact history and household composition are reviewed with the patient. According to the serological status, and following the recommendations of national and international guidelines (9)(14), the following vaccines can be proposed: diphteria/tetanus/acellular pertussis combined vaccine (dTap), inactivated polio vaccine, measles/mumps/rubella combined vaccine (MMR), quadrivalent conjugated meningococcal vaccine, B meningococcal vaccine, conjugated and/or polysaccharidic pneumococcal vaccine, quadrivalent inactivated influenza vaccine, hepatitis B vaccine, varicella vaccine, zoster vaccine, papillomavirus vaccine. If the patient has travel plans, hepatitis A vaccine, yellow fever (YF) vaccine, inactivated typhoid vaccine, and rabies vaccine can be proposed. If a latent TB infection (LTBI) screening test is positive, treatment is started, and the patient is followed to ensure adherence and tolerance until treatment completion. Ivermectin 200 µg/kg single dose is administered during the ImmunoStart consultation of patients originating from hyperendemic areas for *Strongyloides stercoralis*, regardless of the serology result. Household vaccination, frequency of gynecologic and/or dental follow-up, specific preventive measures against *Listeria monocytogenes, Legionella pneumophila*, travel-related diseases or other specific risks are discussed with the patient during consultation.
All patients’ data as well as administered vaccines and drugs are introduced in a specific ImmunoStart database (REDCap Research Electronic Data Capture, Version 8.6.0). We used descriptive statistics to summarize the characteristics of our population. Hypothesis tests for differences between groups were performed using non-parametric Wilcoxon-Mann-Whitney and Kruskal-Wallis tests for continuous variables, and Fisher exact tests for our categorical variables. All our P-values are bilateral and considered statistically significant if <0.05. We used SAS statistical software (version 9.4 SAS institute, Cary North Carolina, USA). The Ethical Committee of CHU Saint-Pierre approved this study (CE/20-07-06).

Results

Between October 2016 and February 2020, 437 patients attended the ImmunoStart consultation (70 in 2017, 193 in 2018, 162 in 2019). They were mainly referred by rheumatologists (56%), dermatologists (25%), and gastroenterologists (18%) and followed up for rheumatoid arthritis (23%), cutaneous psoriasis (20%), psoriatic arthritis (18.5%), ankylosing spondylitis (15%) and Crohn disease (13%). Patient characteristics are summarized in Table 1.

Forty-four percent of patients had already started an immunomodulating treatment before attending the ImmunoStart consultation. Two thirds of the cohort (67%) had travelled or were planning to travel to tropical areas, 62% of whom planned to travel to yellow fever endemic zones.
After checking the serological status and vaccination history, 1380 vaccines were administered to 421 patients (96%) in the context of the ImmunoStart consultation (mean of 3.3 vaccines per patient).

Patients with indication for live attenuated vaccines (LAV) (measles, varicella, yellow fever)

A total of 140 LAV (43 MMR, 89 YF vaccines, 8 varicella vaccines) were administered during ImmunoStart consultation: 45 out of 437 patients (10%) had to reduce or discontinue their immunosuppressive drugs to allow safe LAV administration. No side effect has been observed after the administration of these live attenuated vaccines. Among the cohort, 24 patients (5%) had an indication for one or more LAV administration but presented a formal contraindication because of the treatment with immunosuppressive drug(s). A total of 55 patients (13%) had negative IgG for measles. Of these, 49% were born in Western Europe. Patients younger than 45 years old were more likely to need measles vaccine (p=0.0001). The majority of patients (415/437, 95%) were tested positive for Varicella Zoster virus (VZV) IgG. Patients planning to travel to yellow fever areas (n=182) and needing yellow fever vaccine were more likely to be younger than 45 (p<0.0001) and were less likely to have spent their childhood abroad (p=0.08).

Patients with indications for inactivated vaccines

During the ImmunoStart consultation, 65% of the patients received a combined diphtheria-tetanus-acellular pertussis vaccine. Patients over 45 years of age and originating from North Africa were more likely to need a tetanus booster (p=0.035). 17% (n= 50) of future travelers to tropical areas had negative Hepatitis A IgG. Patients younger than 45 years old and born in Western Europe were more likely to need Hepatitis A vaccine (p<0.0001). Hepatitis B vaccines
were administered to 41 patients in population at risk for this disease. 231 patients (53%) were vaccinated against Influenza and 259 patients were administered pneumococcal vaccine during the ImmunoStart consultation.

Latent Tuberculosis Infection (LTBI) screening

Table 2 summarizes the results of LTBI screening in our cohort. At least one of the 3 LTBI tests was positive in 108 patients (25%). Risk factors for having at least one LTBI positive test were male sex (p=0.007), being born or having lived childhood in Sub-Saharan Africa, Eastern Europe, North Africa (p=0.0021, p=0.0032, and p=0.0008 respectively) and reporting a close contact with somebody diagnosed with TB (p=0.046).

Other screenings

Fourty-six patients (10.6%) originated from hyperendemic zones for Strongyloides stercoralis including 36 who were scheduled to receive corticosteroids, who were treated to prevent Strongyloides stercoralis reactivation. Four patients (0.9%) were started with Hepatitis B reactivation prophylaxis.
Discussion

A large majority (96%) of patients who attended the ImmunoStart consultation needed at least one vaccine. A significant proportion of patients (10%) had to manage a break or reduction in their immunomodulating treatment to receive live attenuated vaccines. Finally, 1 in every 5 patients was treated for LTBI. These results stress the high relevance of preventive consultations such as ImmunoStart, ideally before starting immunosuppression, to facilitate and ensure the quality of future care for IMID patients. CHU Saint-Pierre is a centrally located public hospital in Brussels, accounting for the great diversity of patients’ countries of origin. Therefore, in the context of the ImmunoStart consultation, a large number of patients originate from countries endemic for *Mycobacterium tuberculosis*, Hepatitis B virus or *Strongyloides* for example, highlighting the importance of a robust prevention strategy.

In our experience, 10% of patients had to manage a decrease or a break in their immunomodulating drugs in order to receive a live attenuated vaccine, which could have been avoided if the patient had had a vaccination check-up before starting the immunomodulating drugs. Moreover, the recommendations regarding withdrawal times for immunomodulating drugs, often based on expert opinion rather than on evidence-based or clinical trials, differ greatly from one guideline to another(8)(14). To address this issue, the recent Belgian guidelines were designed to be as adaptable as possible - based on the half-life of immunomodulating drugs - and make it possible to derive a rule applicable to all drugs, past or future(9). Still, LAV administration is challenging in IMID patients. For example, a contraindication to yellow fever vaccination may hamper patients’ possibility to travel (including to visit their families) to yellow fever endemic areas. Concerning measles-containing vaccine, younger patients born in Western Europe were more likely to test
negative for measles IgG. This may be explained by the very little circulation of the measles virus in Western Europe (in Belgium since the 1970s), in contrast to countries outside Western Europe and in the developing countries. Outbreaks of measles in Belgium and in several European countries have been observed in recent years (15). This highly infectious disease can be potentially severe in immunocompromised patients (4). Moreover, access to post-exposure prophylaxis for measles is complicated and extremely expensive in Belgium. Therefore, it is important to particularly target young patients born in industrialized countries for measles IgG screening before starting immunomodulatory drugs.

Hepatitis A can be severe in immunocompromised patients and primary vaccination against hepatitis A during immunomodulating drugs administration has been associated with a high rate of vaccine failures (16). It is therefore also strongly recommended to check generation of IgG after vaccination and/or to apply one of the recently described high dose vaccination regimens (17). From 2021 onwards, the ImmunoStart consultation was also an opportunity to discuss and propose a vaccination schedule against COVID-19 that was best suited to each patient.

As most of IMID patients will beneficiate from TNFα blockers at some point in their disease, we perform the same LTBI screening for all patients attending the ImmunoStart consultation. At the ImmunoStart consultation, we diagnose LTBI according to the ‘either positive strategy’ (6)(18). Probably due to the multicultural nature of our cohort, a high proportion of patients are positive to one of the screening tests. However, this proportion might still be underestimated given the high number of patients already treated by immunosuppressive drugs, which is known to alter results of LTBI screening(19)(20). If screening for TB infection
is to be more precisely targeted, it should focus primarily on male patients, those who were
born or have lived abroad, or those who report having had close contact with a TB patient,
and preferably be carried out before starting immunomodulatory therapy.

Our study has limitations. It should be noted that almost half of the patients of this cohort
were already on immunomodulating treatment at the time of the Immunostart consultation,
and that physicians in some specialties refer patients more systematically than others.
Although it is not perfect, the history, the consultation of vaccination records and the
serological analyses make it possible to assess the vaccination needs of each patient quite
accurately. On the other hand, to our knowledge, this is the first time that the characteristics
of a cohort of patients seen in such a centralized consultation have been reported.
Importantly, ImmunoStart consultations allows infectious disease physicians to acquire
expertise in a constantly evolving field and IMID physicians to have a reference infectious
disease physician for the management of these complex patients. In conclusion, ImmunoStart
consultations provide a centralized and systematic setting for the prevention of infectious
complications in patients with IMID.
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Authors’ contribution: Martin C. created the ImmunoStart consultation in collaboration with Muls V., Brasseur C., Meric de Bellefon L., Lam X., Di Romana S. Martin C. is the head of ImmunoStart clinic. Martin C. collected the data and drafted the initial manuscript. Muls V., Brasseur C., Meric de Bellefon L., Lam X., Di Romana S. and Vanderhilst J. reviewed and edited the manuscript and provided substantial comments.

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Data availability statement: The data that support the findings of this study are available on request from the corresponding author.
Table 1: Summary of the characteristics of the patients attending ImmunoStart consultation (n=437)

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>240 (55)</td>
</tr>
<tr>
<td>Age (y) med (IQR)</td>
<td>44 (34-55)</td>
</tr>
<tr>
<td>Birth region</td>
<td></td>
</tr>
<tr>
<td>- Western Europe</td>
<td>217 (50)</td>
</tr>
<tr>
<td>- Eastern Europe</td>
<td>34 (7,8)</td>
</tr>
<tr>
<td>- North Africa</td>
<td>97 (22)</td>
</tr>
<tr>
<td>- Sub-Saharan Africa</td>
<td>36 (8)</td>
</tr>
<tr>
<td>- Central and South America</td>
<td>23 (5,2)</td>
</tr>
<tr>
<td>- Asia</td>
<td>28 (6,4)</td>
</tr>
<tr>
<td>- North America</td>
<td>2 (0,5)</td>
</tr>
<tr>
<td>Lived more than 10 years in another country</td>
<td>272 (62)</td>
</tr>
<tr>
<td>Lived more than 10 years in region</td>
<td></td>
</tr>
<tr>
<td>- Western Europe</td>
<td>43 (16)</td>
</tr>
<tr>
<td>- East Europe</td>
<td>34 (12,5)</td>
</tr>
<tr>
<td>- North Africa</td>
<td>94 (34,6)</td>
</tr>
<tr>
<td>- Sub-Saharan Africa</td>
<td>43 (15,8)</td>
</tr>
<tr>
<td>- Central and South America</td>
<td>24 (8,8)</td>
</tr>
<tr>
<td>- Asia</td>
<td>33 (12,1)</td>
</tr>
<tr>
<td>- North America</td>
<td>2 (0,7)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>12 (2,4)</td>
</tr>
<tr>
<td>History of close contact with somebody diagnosed with TB</td>
<td>83 (19)</td>
</tr>
<tr>
<td>Do not live alone</td>
<td>336 (77)</td>
</tr>
</tbody>
</table>

Y: years, mo: months, med: median, IQR: interquartile range, TB: tuberculosis
Table 2 Diagnosis of LTBI (positive Mantoux and/or positive IGRA and/or never treated-TB sequelae on Thoracic CT)

<table>
<thead>
<tr>
<th>LTBI test</th>
<th>N total</th>
<th>n positive (% of total cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantoux</td>
<td>383</td>
<td>73 (19)</td>
</tr>
<tr>
<td>IGRA</td>
<td>412</td>
<td>59 (14)</td>
</tr>
<tr>
<td>Lung CT</td>
<td>53</td>
<td>17 (32)</td>
</tr>
</tbody>
</table>

LTBI: latent Tuberculosis infection, IGRA: interferon gamma-release assay, CXR: chest x-ray, CT: computerized tomography

Mean skin induration in positive Mantoux tests was 12 mm.
References


